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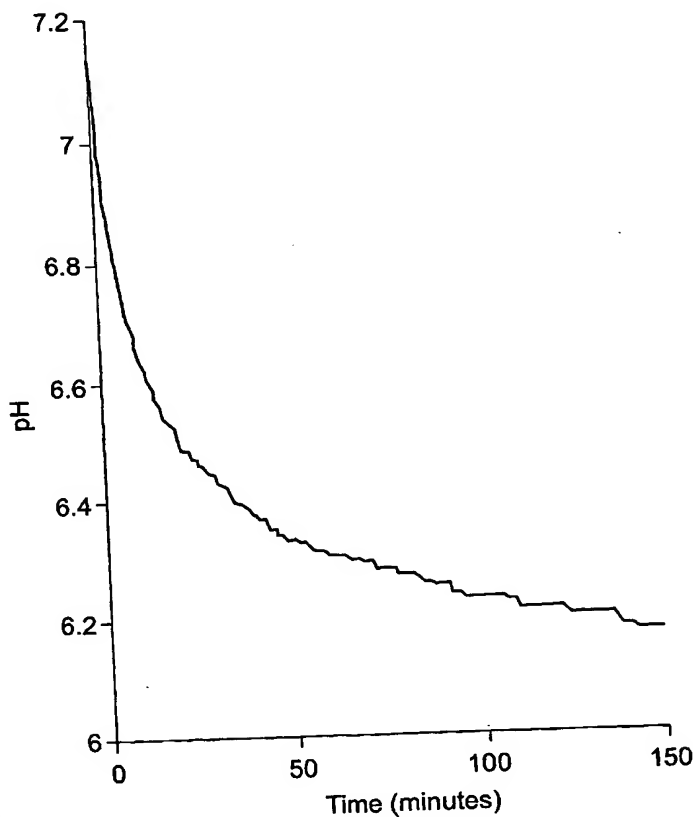
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[Continued on next page]

(54) Title: METHOD AND APPARATUS FOR DETERMINING ISCHAEMIA



(57) Abstract: A method and apparatus for determining information concerning ischaemia using a pH sensor. Embodiments of the invention can be used to determine ischaemia caused by a number of factors, including acute compartment syndrome and vascular disorders, e.g. septicemia.

WO 2004/016162 A1

WO 2004/016162 A1



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1 Method and Apparatus for Determining Ischaemia.

2

3 This invention relates to a method and apparatus for
4 measuring intracompartamental pH, and especially but
5 not exclusively to measuring intracompartamental and
6 intramuscular pH for the diagnosis of ischaemia, and
7 especially Acute Compartment Syndrome.

8

9 Ischaemia is the reduction or cessation of blood
10 flow to various parts of the body, leading to an
11 insufficiency in local availability of the oxygen
12 and metabolites normally carried by the blood.
13 Ischaemia can arise locally from e.g. bone fractures
14 causing local swelling in a limb which increases the
15 distances between the cells and the arteries,
16 thereby decreasing the effectiveness of the delivery
17 of the oxygen and the metabolites from the blood.
18 At the same time, the blood vessels are compressed
19 due to the swelling, further reducing their capacity
20 to deliver the nutrients and oxygen. Surgery also
21 involves a risk of ischaemia, when blood vessels are
22 severed during the procedure, either deliberately

1 during the transplant of a free flap, or
2 accidentally during the cutting procedure.
3 Ischaemia can also arise chronically. Ischaemia can
4 also arise from trauma at a remote site of the body.
5 For example, a limb can become ischaemic when the
6 blood flow is diverted from the limb back to the
7 trunk of the body in response to central organ
8 dysfunction or abdominal infection that could be
9 remote from the site of ischaemia.

10

11 There are various kinds of ischaemia and among these
12 Acute compartment syndrome (ACS) is a surgical
13 emergency which if not recognised early may lead to
14 crippling deformities, loss of limb or even death.

15

16 Compartment syndrome has been defined as "a
17 condition in which increased pressure within a
18 limited space compromises the circulation and
19 function of tissues in that space"¹. It is most
20 commonly seen following injuries of the leg but may
21 also occur in the upper limb, and following
22 ischaemic re-perfusion injuries and burns.
23 Furthermore, sub-clinical compartment syndromes have
24 occurred following reaming of the medullary canal in
25 the nailing of long bone fractures². Early
26 diagnosis and prompt surgical intervention is
27 essential to avoid the complications which may
28 ensue. These include neurological deficit, muscle
29 necrosis, acute renal failure, amputation and loss
30 of life. Currently, the diagnosis of acute
31 compartment syndrome is based on clinical assessment
32 and intra-compartmental (IC) pressure monitoring.

1 Extreme pain exacerbated by passive stretching of
2 the muscles in the compartment and paraesthesia are
3 the most reliable signs, but may only become
4 apparent in the later stages of acute compartment
5 syndrome, and are not reliable in the unconscious,
6 neurologically impaired or paediatric patient. In
7 these circumstances invasive methods of monitoring
8 IC pressure are therefore deemed essential³.

9

10 Compartment pressure monitoring has been advocated
11 since 1975⁴. There are a number of pressure
12 monitors available but most rely on a column of
13 fluid leading to inaccuracies.

14

15 The invention also provides a method of determining
16 the presence or severity of ischaemia in a tissue,
17 the method comprising the steps of inserting a pH
18 sensor into the tissue, and measuring the
19 intracompartmental pH in the tissue.

20

21 Typically the tissue is muscle.

22

23 Typically, the method is used in the diagnosis of
24 Acute Compartment Syndrome. Typically, the acute
25 compartment syndrome is caused by a fractured limb.

26

27 The pH of muscle is a good indicator of its
28 metabolic state with a normal physiological range of
29 6.95 to 7.2⁵. As the pressure in the compartment
30 increases, blood flow ceases and lactic acid builds
31 up, reducing the pH. By using a method of observing
32 the changing pH of skeletal muscle tissue, it is

1 possible to identify muscle which is at risk of
2 irreversible damage prior to the development of
3 clinical signs.

4
5 A second probe may also be provided to measure the
6 intracompartmental pressure; the pH and pressure
7 measurements can be used in conjunction to provide a
8 diagnosis.

9
10 Preferably, the or each sensor is mounted on a
11 respective catheter. Preferably, the or each
12 catheter is inserted into the muscle through a
13 respective cannula.

14
15 Preferably, the or each cannula is inserted into
16 skeletal muscle in an orientation that is generally
17 parallel to the muscle fibres. Preferably, the or
18 each cannula is inserted into the muscle adjacent
19 to, but not communicating with, the fracture site.

20
21 Preferably, the or each sensor is monitored
22 continuously for at least 24 hours.

23
24 Preferably, the reading from the or each sensor is
25 compared with a calibrated scale to determine the
26 extent of muscle damage. Typically, the reading
27 from the or each sensor is used to determine the
28 appropriate treatment, e.g., a fasciotomy. If the
29 damage is caught early enough, a fasciotomy may be
30 avoidable and intermittent pneumatic compression
31 treatment or other conservative treatments may be
32 sufficient.

1

2 According to a second aspect of the present
3 invention, there is provided apparatus for
4 determining the presence or severity of ischaemia,
5 the apparatus including a pH sensor adapted to be
6 inserted into a muscle.

7

8 Preferably, the apparatus is suitable for use in
9 providing information concerning soft tissue,
10 physiological changes and pathological conditions,
11 such as septicaemia, pancreatitis and other blood
12 disorders and conditions. Preferably, the
13 apparatus is suitable for use in the diagnosis of
14 Acute Compartment Syndrome.

15

16 Preferably, the pH sensor is mounted on a catheter.
17 Typically, the catheter is glass-tipped.
18 Preferably, the glass is durable, heat-strengthened
19 and fracture-proof.

20

21 Alternatively, the catheter is antimony-tipped.

22

23 The pH sensor and the pressure sensor can be mounted
24 on the same catheter.

25

26 Optionally, the apparatus also includes a pressure
27 sensor. Optionally, the pH sensor is connected to a
28 pH recorder. Preferably, the pressure sensor is
29 connected to a pressure monitoring system.

30

31 Typically, the pressure sensor is mounted on a
32 second catheter. Alternatively, both the pH sensor

1 and the pressure sensor are mounted on the same
2 catheter. In this case, the pressure sensor and the
3 pH sensor are preferably connected to the same
4 monitoring system, which monitors and records both
5 pressure and pH.

6
7 Optionally, two or more pH sensors are provided.
8 Optionally, two or more pressure sensors are
9 provided.

10
11 According to a third aspect of the present
12 invention, there is provided the use of a pH sensor
13 device for the determination of the presence or the
14 severity of ischaemia and typically Acute
15 Compartment Syndrome.

16
17 According to a fourth aspect of the present
18 invention, there is provided a pH sensor device
19 adapted to diagnose ischaemia, and typically Acute
20 Compartment Syndrome.

21
22 The invention also provides a method of determining
23 information concerning the condition of soft tissue,
24 the method comprising the steps of inserting a pH
25 sensor into the soft tissue and measuring the pH in
26 the tissue.

27
28 According to the present invention, there is also
29 provided a method of measuring intracompartamental
30 pH, including the step of inserting a pH sensor
31 directly into a muscle.

32

1 The method can be used to provide information about
2 ischaemia arising from localised damage and remote
3 trauma alike, as the pH measurement gives an
4 accurate information about localised ischaemia,
5 thereby allowing the method to be used for providing
6 information about ischaemia arising from a wide
7 variety of different causes.

8

9 An embodiment of the invention will now be described
10 by way of example only and with reference to the
11 following drawings, in which:-

12

13 Fig 1 shows a side view of a catheter with a pH
14 monitor mounted thereon;

15 Fig 2 shows a partial cross-section of a
16 fractured limb, into which catheters with
17 sensors are inserted;

18 Fig 3a shows a graph of pH as a function of
19 time for example 1 during tourniquet inflation;

20 Fig 3b shows a graph of the mean pH changes
21 from the Fig 3a graph;

22 Fig 4a shows a graph of pH as a function of
23 time for example 1 following release of
24 tourniquet;

25 Fig 4b shows a graph of the mean pH changes
26 from the Fig 4a graph;

27 Fig 5 shows a graph of pH and pressure as
28 functions of time for a patient with Acute
29 Compartment Syndrome;

30 Fig 6 shows a graph of pH and pressure as
31 functions of time for a patient who did not
32 have Acute Compartment Syndrome;

1 Fig 7 shows a graph of pH and delta pressure
2 (diastolic blood pressure minus IC pressure) as
3 functions of time for the patient of Fig 5;
4 Fig 8 shows a graph of pH and delta pressure
5 (diastolic blood pressure minus IC pressure) as
6 functions of time for the patient of Fig 6;
7 Fig 9 shows a graph of pH against time for
8 example 1 upon inflation of the tourniquet;
9 Fig 10 shows a graph of pH against time for
10 example 1 upon deflation of the tourniquet;
11 Fig 11 shows a graph of ICP against time for
12 example 4;
13 Fig 12 shows a graph of delta pressure against
14 time for example 4;
15 Fig 13 shows a graph of pH against time for
16 example 4;
17 Fig 14 shows a graph of ICP against time for
18 the patients of example 4 undergoing
19 intramedullary nailing;
20 Fig 15 shows a graph of delta pressure against
21 time for the patients of example 4 undergoing
22 intramedullary nailing;
23 Fig 16 shows a graph of ICP against time for
24 the patients of example 4 undergoing
25 intramedullary nailing, showing results for
26 patients with ACS and for those without ACS;
27 Fig 17 shows a graph of pH against time for the
28 patients of example 4 undergoing intramedullary
29 nailing, for patients with ACS and for those
30 without ACS;

1 Fig 18 shows a graph of ICP and pH against the
2 time of certain events of fasciotomies for
3 patients of example 4;
4 Fig 19 shows a graph of ICP against time for
5 the full group of patients in example 4,
6 showing results for both patients with ACS and
7 without ACS;
8 Fig 20 shows a graph of delta pressure against
9 time for the full group of patients in example
10 4, showing results for both patients with ACS
11 and without ACS;
12 Fig 21 shows a graph of pH against time for the
13 full group of patients in example 4, showing
14 results for both patients with ACS and without
15 ACS;
16 Fig 22 shows a ROC curve for pH for the
17 patients of example 4;
18 Fig 23 shows a ROC curve for ICP for the
19 patients of example 4;
20 Fig 24 shows a ROC curve for delta pressure for
21 the patients of example 4;
22 Fig 25 shows a ROC curve for initial ICP for
23 the patients of example 4;
24 Fig 26 shows a ROC curve for initial delta
25 pressure for the patients of example 4;
26 Fig 27 shows a ROC curve for initial pH for the
27 patients of example 4;
28 Fig 28 shows a graph of pH decline over time
29 during muscle ischaemia;
30 Fig 29 shows a graph of G6P decline over time
31 during muscle ischaemia;

Fig 30 shows a graph of lactate concentration increase over time during muscle ischaemia;
Fig 31 shows a graph of pyruvate concentration decline over time during muscle ischaemia;
Fig 32 shows a plot of intramuscular (measured) pH values against calculated pH values;
Fig 33 shows a measurement of agreement curve of the Fig 32 data;
Figs 34, 35 show graphs of the decline in ATP and PCr respectively over time during muscle ischaemia;
Figs 36 and 37 show graphs of muscle pH measured in a patient with acute on chronic ischaemia; and
Fig 38 shows similar data for another patient with chronic ischaemia.

Fig 1 shows a sterile 1.5mm glass-tipped (Mettler Toledo) catheter 1 (made of durable, heat-strengthened, fracture-proof glass). A pH sensor probe 5 is mounted on the tip of the catheter 1.

A glass pH catheter was chosen specifically for this study as these catheters have been shown to maintain a high accuracy of muscle pH recordings, with very little drift over time. They have no recorded ill effects and are easily sterilised to surgical standards as described below.

Fig 2 shows a portion of a lower leg of a patient into which is inserted the catheter 1 of Fig 1. The catheter is inserted into skeletal muscle in the

1 proximity of a fracture in the patient's tibia. The
2 catheter 1 is connected to a pH recorder 10 via a
3 sterilised adapter cable 15. A suitable pH recorder
4 is the Flexilog 2010 dual-channel pH recorder
5 (Oakfield instruments), which permits continuous
6 monitoring of intracompartmental (IC) pH, accurate
7 to one decimal place, at intervals of one second.
8 The monitor also typically has a marker facility
9 built in to allow events to be registered during the
10 recording time.

11
12 Fig 2 also shows a second catheter 2 connected to a
13 pressure monitoring system 11, which is used to
14 continuously monitor IC pressure. A suitable system
15 is the Kodiag mobile pressure monitoring system (B
16 Braun), which allows more accurate monitoring of
17 pressure compared with other available devices⁵, and
18 is also easy to use and sterilise. The Kodiag
19 monitoring system consists of a probe with a steel
20 encased tip, which converts the pressure signal to
21 an electrically useable signal, and is attached via
22 an extension cable to the Kodiag measuring unit
23 which then evaluates and displays the measured
24 values. This system is capable of measuring pressure
25 within a range of 0 to 199 mmHg, accurate to +/- 1
26 mmHg.

27 28 General Methods

29 The pH unit is calibrated prior to each use. The
30 unit has a calibration procedure built in which uses
31 pH buffers of 7.0 and 1.1 to ensure that accurate
32 readings are obtained with each individual. A

1 circuit is created with the unit, the catheter, and
2 the patient using an external reference electrode
3 (ECG pad) and each buffer in turn. Following each
4 patient's study, this circuit is re-created using
5 the 7.0 buffer to obtain a reading, and therefore
6 the value of any drift that has occurred during
7 recording.

8
9 The pH probe and cable are sterilised to surgical
10 standards, i.e. using a Tristel sterilisation bath.
11 Further details of appropriate sterilisation
12 procedures are given in the examples below.

13
14 The pressure probe is sterilised to surgical
15 standards as per Kodiag instruction manual using
16 steam sterilisation to a maximum temperature of
17 134°C.

18
19 The pH and pressure monitors are placed in the
20 muscle through anaesthetised, surgically sterile
21 skin. The catheters 1, 2 are inserted, typically
22 through 14 gauge Adsyte intravenous cannulas placed
23 generally parallel to the muscle fibres, and
24 adjacent to each other, into the muscle compartment
25 adjacent to, but not communicating with, the
26 fracture site. The catheters should be inserted at
27 a safe site, away from the position of impending
28 incisions. The angle of insertion is typically
29 approximately 30° to the skin.

30
31 If the apparatus is being used to diagnose suspected
32 acute compartment syndrome caused by a tibial shaft

1 fracture, the probes are typically inserted into the
2 anterior compartment of the lower leg. For a
3 femoral shaft fracture, the probes are typically
4 inserted into the lateral portion of the anterior
5 compartment of the thigh.

6
7 Upon penetration of the fascia in a distal
8 direction, the catheter is levelled out and further
9 advanced to its limit. The needle is then removed
10 and the probe inserted through the lumen of the
11 plastic sheath to a distance of approximately 1 cm
12 beyond the tip of the sheath into the muscle belly.
13 The probe and cannula are then typically secured
14 with a clear adhesive dressing. The external
15 reference electrode is then connected to the
16 patient's limb, and both the pH probe and the
17 external reference cable are then connected to the
18 monitor and record mode 2 selected, at a desired
19 measurement rate.

20
21 Optionally, other parameters may be measured
22 simultaneously, for example blood pressure, oxygen
23 saturation and end tidal carbon dioxide. Suitable
24 recording devices for these parameters include the
25 Critikon Dynamap 1846 SX, the Ohmeda Biox 3740 pulse
26 oximeter, and the Captronic Ultra ETCO2 monitor
27 respectively.

28
29 These parameters are measured at a desired interval,
30 for example every five minutes. The blood pressure
31 measurements allow "delta pressure" to be calculated
32 (diastolic blood pressure minus IC pressure). A

1 sustained delta pressure value of 30mmHg or less is
2 currently the most frequently used indicator for
3 surgical intervention⁴.

4
5 Intracompartmental pressure and pH are recorded
6 continuously for at least 24 hours post-injury or
7 for longer as clinically indicated. The marker
8 facility is used as required, to record individual
9 events during the recording time.

10
11 Following the completion of the measurements, both
12 probes are removed, pressure applied to the puncture
13 sites, and a small gauze dressing applied to the
14 puncture wounds. Each probe is then wiped clean
15 with a damp cloth ready for calibration. A post-
16 recording calibration is then undertaken, which is
17 identical to the calibration procedure prior to use.

18
19 The information collected is then downloaded into a
20 software package, for example, the Flexisoft III
21 software package, and the recorder's memory is then
22 cleared, ready for future use.

23
24 After 25 uses, each pressure probe is returned to
25 the manufacturers for recalibration, as recommended
26 by the manufacturers.

27
28 Example 1

29 The aims of this example were to demonstrate the
30 ability of the pH monitor to record intramuscular pH
31 in a situation of changing acidity resulting from

1 tourniquet ischaemia , and the suitability and ease
2 of use of the pH recorder in human skeletal muscle.

3
4 Over a period of five months, patients admitted to
5 the elective orthopaedic unit of a local hospital
6 were invited to participate. These comprised two
7 groups, viz.:

- 8 1. elective knee arthroscopy (27)
- 9 2. elective total knee replacement surgery (12)

10
11 The pH monitor was calibrated on each patient in the
12 ward prior to arrival in theatre.

13
14 The pH probe and cable were sterilised to surgical
15 standards in a Tristel 700 sterilisation bath. Five
16 litres of Tristel 700 was mixed with 500mls of
17 activator in a sterilising bath once a week. When
18 required, the probe was fully submerged in the bath
19 for 10 minutes, as recommended in the Tristel
20 guidelines. It was then rinsed in sterile water, and
21 placed on a prepared sterile trolley ready for use.

22
23 Once general (or spinal) anaesthesia had been
24 induced, a tourniquet was placed on the appropriate
25 thigh (but not inflated), an external reference
26 electrode was placed on the lateral thigh of the
27 operative leg, and the surgical site was prepared
28 and draped in a routine fashion.

29
30 The pH probe was inserted into the mid-portion of
31 tibialis anterior of the appropriate leg,
32 approximately 5cm below and 1-2cm lateral to the

1 tibial tubercle. The probe was then connected to
2 the Flexilog recorder and an interval of one second
3 per measurement was selected. An initial end tidal
4 carbon dioxide level was noted at this point (prior
5 to tourniquet inflation) for the patients having a
6 general anaesthetic. The leg was then elevated for
7 three minutes and the tourniquet was subsequently
8 inflated to 250-300mmHg; the marker facility was
9 used to mark the inflation of the tourniquet. Blood
10 pressure, oxygen saturation and pH were then
11 recorded at intervals of 5 minutes during the
12 surgery.

13

14 After all of the measurements had been taken, the
15 tourniquet was deflated. The marker facility was
16 used to mark the deflation of the tourniquet. The
17 probe remained in situ for 20 minutes after
18 arthroscopy (AX) and 30 minutes after knee
19 replacement (TKR) after tourniquet deflation, during
20 which time the muscle pH, blood pressure and
21 peripheral oxygen saturation continued to be
22 recorded at 5-minute intervals.

23

24 Following the end of recording and removal of the
25 probe from each patient, the probe was checked to
26 detect any drift in the system that had occurred
27 during recording. This involved creating a circuit
28 by the placement of the probe and the patient's
29 finger in the 7.0 buffer, with the external
30 reference electrode still connected to the thigh,
31 and noting the recorded value at 1 minute.

32

1 Example 2

2 A 26 year old male was admitted to the Intensive
3 Therapy Unit following a road traffic accident, with
4 generalised cerebral swelling and a closed fracture
5 of his right tibia and fibula (Tscherne C3). Intra-
6 compartmental monitoring of pH, ICP and monitoring
7 of diastolic blood pressure within the right
8 tibialis anterior began 11 hours post injury prior
9 to transfer to theatre for intramedullary nailing.
10 Clinically, the leg appeared very swollen and tight,
11 but no subjective data was available as he was
12 ventilated and sedated for his head injury.
13 Following intramedullary nailing of the tibial
14 fracture, concern was raised as to the presence of
15 ACS, and ICP monitoring had revealed a delta
16 pressure (diastolic blood pressure - ICP) of 30 or
17 less prior to, and throughout his surgery (current
18 guideline for diagnosis of ACS). Full four
19 compartment fasciotomies were performed and bulging,
20 boggy muscle was revealed, with some dark areas of
21 muscle suggesting ischaemia. On return to theatre
22 48 hours later, the muscle appeared healthy, several
23 small open biopsies were taken, and the wounds were
24 closed with split skin grafts. Clinically he had no
25 residual signs or symptoms attributable to ACS at
26 his 8 week follow up appointment.

27

28 Example 3

29 A 19 year old male sustained an open fracture of the
30 left tibial shaft (Gustilo I) when he was knocked
31 off his pedal bike. Monitoring of muscle pH, ICP
32 and diastolic blood pressure commenced in theatre

1 following anaesthesia and wound debridement
2 following the method described above, to maintain
3 sterility.

4

5 Example 4

6 Over approximately six months, patients admitted to
7 a local hospital, with a fracture involving the
8 diaphysis of the tibia or femur, a crush injury, or
9 a suspected compartment syndrome at any anatomical
10 site, were invited to take part in this study. All
11 patients suffering from the above injuries during
12 the study period were approached to take part,
13 subject to fulfilling ethical entry criteria.
14 Subjects underwent intra-compartmental monitoring of
15 pressure and muscle pH for up to 48 hours. In
16 addition, muscle biopsies were obtained from those
17 patients having a surgical procedure under general
18 anaesthesia. Information pertaining to patient
19 demographics, current injury, and relevant past
20 medical history was collected from their casualty
21 cards, medical notes and radiological
22 investigations.

23

24 The trauma group included 61 patients admitted to
25 the orthopaedic unit/intensive care unit, suffering
26 from one or more of the following injuries:

- 27 1. Tibial shaft fractures
- 28 2. Long bone fractures of the lower limb requiring
29 intramedullary nailing
- 30 3. Acute compartment syndrome, at any anatomical
31 site, diagnosed by the patient's medical team
32 with currently accepted methods

1 4. Crush injuries

2

3 As the admission of trauma patients is not as
4 predictable as elective admissions, and cold
5 sterilising techniques were not regularly used in
6 the trauma theatre, the pH probe and cable were
7 sterilised in a Tristel One Day concentrate bath.
8 On each occasion requiring the use of the
9 sterilisant, 25mls of each liquid were mixed with
10 950ml of plain tap water. A tester kit was used to
11 ensure an effective sterilisant was produced and the
12 probe was submerged for the recommended 5 minutes.
13 The solution was then discarded after only one use.

14

15 The pH and pressure probes were inserted into the
16 appropriate muscle compartment within 5cm of, but
17 not communicating with, the fracture site / within
18 the site of the crush injury. If the probes were
19 placed prior to fracture fixation, they were
20 inserted within a long sterile plastic bag, to
21 ensure continuing sterility of the wider surgical
22 field during the ensuing procedure. The Flexilog
23 system was set up to record pH at six second
24 intervals to allow recording to continue for up to
25 96 hours.

26

27 The probes were introduced parallel to each other in
28 adjacent sites within the same fascial compartment:
29 the anterior compartment of the lower leg for tibial
30 fractures; the lateral compartment of thigh for
31 femoral fractures, and the appropriate site for
32 suspected compartment syndromes at other anatomical

1 regions . In those patients who were not undergoing a
2 general anaesthetic in the next few hours , a local
3 anaesthetic used to anaesthetise the skin alone was
4 used at the site of cannula entry . Once compartment
5 monitoring commenced , the ICP , muscle pH , blood
6 pressure and peripheral oxygen saturation were
7 recorded at 5 minute intervals during surgery , then
8 hourly for the duration of the study . For those
9 patients treated with a Plaster of Paris cast , the
10 probes were inserted under local anaesthetic (as
11 above) , prior to the application of a full leg cast ,
12 and a window was created in the plaster over the
13 probe site to allow removal of the probes upon
14 completion of the studies .

15

16 For those with tibial and femoral shaft fractures
17 treated with intramedullary nails , a further
18 protocol was introduced during the operation . The
19 marker facility was used to mark those events during
20 surgery which were related to fracture fixation and
21 fasciotomies . All parameters were recorded on the
22 patient's chart at the following points :

- 23 1. Pre-anaesthetic
- 24 2. Post-anaesthetic
- 25 3. Traction application
- 26 4. Guidewire insertion
- 27 5. Reaming of the medullary canal
- 28 6. Intramedullary nail insertion
- 29 7. Post nail insertion
- 30 8. Fracture impaction
- 31 9. Post-traction release
- 32 10. Recovery room

1 For those patients suspected clinically of having a
2 compartment syndrome and taken to theatre for
3 fasciotomies, the marker facility was used to mark
4 the following events:

- 5 1. Induction of anaesthetic
- 6 2. Appropriate skin and fascial incisions
- 7 3. Decompression of each compartment (4)
- 8 4. Recovery

9
10 Blood pressure and peripheral oxygen saturation were
11 monitored. During anaesthetic time using an
12 endotracheal tube or laryngeal mask, the patient's
13 end tidal carbon dioxide (ET CO₂) was recorded.
14

15 During their stay in hospital, all of the patients
16 were regularly assessed clinically for evidence of
17 pain on passive stretch, muscle weakness and sensory
18 changes in the injured limb to identify the presence
19 of a developing acute compartment syndrome. In
20 addition, all of the patients who underwent
21 fasciotomies for suspected compartment syndrome, had
22 a clinical intra-operative assessment of muscle
23 damage performed and recorded. This included
24 visualisation of the state of the muscle within the
25 compartment as the fascia was incised, with colour,
26 obvious bulging, oedema, necrosis and muscle twitch
27 response recorded appropriately.
28

29 Example 5

30 This example examines an ischaemic mammalian muscle
31 model, to review and compare the underlying
32 biochemistry, immunocytochemistry, and

1 histochemistry of muscle ischaemia to muscle pH
2 measurements, to verify the intramuscular (IM) pH
3 readings, and to identify "critical pH" levels for
4 skeletal muscle, beyond which point irreversible
5 tissue damage occurs.

6
7 Methods for example 5:

8 Male rats were sacrificed through stunning and neck
9 fracture and Ischaemia time was noted. They were
10 placed in an incubator, maintained at 37°C. The
11 quadriceps femoris muscle was exposed atraumatically
12 and a 1.5mm diameter, glass tipped, single channel
13 pH catheter (M1.5; M.I.C. France), connected to a
14 2020 Flexilog pH monitor (Oakfield Instruments, UK)
15 was employed to monitor muscle pH. This system
16 required an Ag/AgCl external reference probe.
17 Before and after use the monitor was calibrated at
18 pH 1.1 and pH 7, and drift was found to be minimal.
19 The pH catheter was cleaned between usages with an
20 alcohol-based solution, and prior to use was
21 thoroughly irrigated with saline. Following
22 exposure of the quadratis femoris muscle, the pH
23 catheter, through a 12 gauge cannula and the
24 external reference probe were inserted into the
25 exposed muscle belly. At predetermined pH levels
26 muscle biopsies were taken under direct vision.
27 These samples were snap frozen in liquid N₂. The
28 samples were stored at -80°C, prior to freeze-
29 drying. A commercially available freeze-drier was
30 used and the samples stored in a desiccator at -
31 10°C.

32

1 Immediately prior to analysis, the samples were
2 pulverised with an agate pestle and mortar and the
3 connective tissue was removed. The remaining muscle
4 powder was thoroughly pulverised and two 10mg
5 samples were weighed into disposable plastic
6 centrifuge tubes for extraction and analysis.

7
8 Muscle metabolites were extracted with cold 0.5 N
9 perchloric acid containing 1mmol/l EDTA at a ratio
10 of 1ml perchloric acid for every 12.5mg of muscle
11 powder. This solution was agitated in an ice bath
12 for ten minutes and then centrifuged for 60 seconds.
13 The supernatant was removed and neutralised by the
14 addition of a one-fourth volume of 2.1 mol/l KHCO_3 .

15 16 Assays

17 The concentrations of Glucose-6-Phosphate (G6P),
18 Lactate and Pyruvate, expressed as millimoles per
19 kilogram of dry muscle were assayed by modifications
20 of the method of Olsen⁸. Fluorometric measurements
21 were made on a filter fluorimeter (Locarte model LF
22 8-9: Locarte, London, UK). All fluorimetric analyses
23 were conducted using standard solutions that had been
24 calibrated photometrically.

25
26 Glucose-6-Phosphate was assayed in the presence of
27 100mmol/l Tris buffer, pH 8.1; 5mmol/l NADP; and G-
28 6-P Dehydrogenase, 10 U/ml.

29 Lactate was assayed in the presence of 1.1 mol/l
30 Hydrazine buffer, pH 9.0; 5 mmol/l NAD; and Lactate
31 Dehydrogenase, 2750 U/ml.

1 Pyruvate was assayed in the presence of 0.5 mol/l
2 Phosphate buffer, pH 7.0; 2 mmol/l NADH; and Lactate
3 Dehydrogenase, 5.5 U/ml.

4
5 In each case the reaction mixture containing buffer,
6 cofactor and enzyme was prepared immediately prior
7 to use. By keeping the reaction volume small,
8 favourable kinetics were ensured. All incubations
9 were carried out at room temperature, samples and
10 standard solutions being treated identically.

11
12 At the end of the incubation period the sample was
13 diluted by the addition of 1 ml of H₂O. The
14 fluorescence was then read; for G6P and lactate the
15 blank was set to zero; for pyruvate the highest
16 standard solution was set to zero. Sample values
17 were obtained by comparison with the standard curve
18 and the corrected for the dilutional effects of the
19 extraction. ATP and PCr were assayed using
20 modifications to the original methods described by
21 Harris⁷. Spectrophotometric measurements were made on
22 an Eppendorf photometer (Model 1101M,
23 wavelength=334nm).

24
25 ATP and PCr were assayed sequentially in the
26 presence of 50mmol/l TEA buffer, pH 7.5; 0.1 mol/l
27 Magnesium Chloride; 0.5 mol/l Glucose; 22mmol/l ADP;
28 5mmol/l NADP; G6P Dehydrogenase, 10U/ml; Hexokinase,
29 50U/ml; and Creatine Kinase 90U/ml.

30
31 Analysis of ATP and PCr were made on the same day as
32 extraction.

1

2 Example 6

3 The aim of this example was to demonstrate the
4 ability to monitor the muscle pH changes associated
5 with limb ischaemia, in both the acute and the
6 chronic forms. In vascular surgery there are a
7 number of novel uses for pH monitoring including
8 assisting in the decision to re-vascularise
9 compromised limbs or to primarily amputate to avoid
10 the potentially life threatening systematic effects
11 of re-vascularisation.

12

13 The calibration, sterilisation and insertion
14 techniques used in this study were identical to
15 those described above in the method section.
16 Markers were used in this instance during surgery
17 for clamping of the artery (ON), release of the
18 clamp (OFF), return to full circulation (CIRC) and
19 in some cases, during the angiogram (ANGIO) used to
20 check graft patency.

21

22 Results for Example 1

23 The following analyses were conducted on the results
24 from a subgroup of the patients; 24 patients
25 undergoing elective knee surgery and 8 patients
26 undergoing elective total knee replacement surgery.

27

28 Arthroscopy study group

29 This example covered eighteen men and seven women
30 (mean age of 41 years, mean tourniquet time of 21
31 minutes). The mean muscle pH before the tourniquet
32 was inflated was 6.9. This decreased by 0.3 to 6.6

1 prior to the tourniquet being released. Fifteen
2 minutes after the tourniquet was deflated the muscle
3 had recovered by an average of 0.16 of a pH unit to
4 6.76.

5
6 Total knee replacement study group (see figs 3 and
7 4).

8 This group of patients included 3 males and 5
9 females (mean age of 68 years, mean tourniquet time
10 of 79 minutes). The mean pH prior to tourniquet
11 inflation was slightly lower than the arthroscopy
12 group at 6.7, and decreased to 6.2 before the
13 tourniquet was released. Fifteen minutes later,
14 muscle pH had recovered by 0.28 of a pH unit to
15 6.48, with further recovery of 0.16 to 6.64 by 30
16 minutes (total recovery of 0.44).

17
18 The average pH recorded prior to release of the
19 tourniquet in the knee replacement group was 6.3.

20
21 The remaining analyses of Example 1 cover the full
22 group of 27 patients undergoing elective knee
23 arthroscopies and 12 patients having total knee
24 replacements.

25
26 Statistical analysis of the results was completed
27 using SPSS for windows, version 10.0 (Microsoft).
28 Non-parametric statistical tests were used due to
29 the skewed distributions of the samples. For
30 correlations between continuous data, Spearman's rho
31 correlations were employed. For comparisons of
32 categorical data with continuous data, Mann-Whitney

1 tests were used. When looking for significant
2 changes over time, Wilcoxon matched pairs testing
3 was carried out.

4
5 Table 1.1 shows the general descriptive data
6 gathered for Example 1. The group has been sub-
7 divided into two sets, those who underwent knee
8 arthroscopy, and therefore had a relatively short
9 period of tourniquet ischaemia, and those who had
10 total knee replacement surgery (TKR), and therefore
11 required prolonged use of the tourniquet.

12
13
14 **Table 1.1: General descriptive data**

Category	Whole Group N=39	Arthroscopy n=27	TKR N=12
Male	25	19	6
Female	14	8	6
Mean Age (years)	48	40	68
Mean Tourniquet time (minutes)	37	21	74
Tourniquet Pressure 30OmmHg	33	21	12
Tourniquet Pressure 25OmmHg	6	6	0

15
16 The mean change in pH during tourniquet ischaemia
17 for each sub-group is displayed in figure 9. In the
18 arthroscopy group, the mean muscle pH prior to
19 tourniquet inflation was 6.80. This decreased to
20 6.58 prior to the tourniquet being released, and
21 recovered to 6.66 in fifteen minutes. Although the
22 mean pH prior to tourniquet inflation was slightly
23 lower in the total knee replacement group (6.74),
24 the difference was not statistically significant
25 (table 2). However, the pH decreased to 6.35 prior

to tourniquet release in the knee replacement group, which was significantly different from the arthroscopy group (table 1.2). Fifteen minutes after tourniquet release, the muscle pH in the TKR group had recovered to 6.51, with further recovery to 6.63 by 30 minutes. In the whole group, recovery to baseline pH was achieved within 30 minutes following release of the tourniquet ($z=-1.232$; $p=0.218$).

Using the whole group, several factors, including age, gender, initial end tidal carbon dioxide, and the tourniquet inflation pressure, were analysed as to their effects on either the baseline muscle pH recorded prior to tourniquet inflation, the change in pH occurring during tourniquet ischaemia, or during recovery (Table 1.2). No one factor had a significant influence on the results.

Table 1.2: The effect of various factors on the initial pH, and changes in pH occurring during ischaemia and recovery

	Age*	Gender†	Surgery†	Tpressure†	ETCO2*	Side†
Baseline Ph	cc=0.063 p=0.720	Z=-0.511 P=0.609	z=-0.901 p=0.368	z=-1.696 p=0.090	cc=0.112 p=0.650	z=-1.167 p=0.243
Ischaemic pH change	cc=-0.237 p=0.159	Z=-0.840 P=0.401	z=-3.034 p=0.002* *	z=-0.725 p=0.468	cc=0.152 p=0.524	z=-0.201 p=0.841
Recovery 0-15 minutes	cc=-0.009 p=0.961	Z=-0.218 P=0.827	z=-0.847 p=0.397	z=-0.669 p=0.504	cc=0.082 p=0.731	z=-0.699 p=0.484
Recovery 15-30 minutes	cc=-0.222 p=0.595	Z=-0.833 P=0.405			cc=0.949 p=0.051	z=-1.725 p=0.084

* Spearman's rho correlations cc=correlation coefficient

1 † . Mann Whitney tests

2 **Significant to the 0.01 Level

3
4 The mean recorded value in the drift measurement was
5 7.07 (SD 0.28) for the whole group, which does not
6 represent a significant drift during recording ($z=-$
7 1.211, $p=0.226$).

8
9 It was found that placement of the external
10 reference electrode close to the probe insertion
11 site resulted in the best recordings.

12
13 The pH decreased during the period of tourniquet
14 inflation and recovered upon release.

15
16 Statistical analysis revealed a linear pattern of pH
17 decline upon inflation of the tourniquet (Fig 9).
18 Furthermore, Wilcoxon ranked pairs testing found no
19 significant differences between the reduction in pH
20 for each 5-minute interval during this trial. The
21 change in muscle pH was significant following just 5
22 minutes of tourniquet ischaemia ($p<0.001$).

23
24 Upon release of the tourniquet, the intramuscular pH
25 increased (Fig 10). However, it remained
26 significantly different from baseline pH values
27 until 20 minutes after the tourniquet was removed in
28 the arthroscopy group, and 25 minutes of re -
29 perfusion in the knee replacement group. This is
30 thought to reflect the prolonged tourniquet time in
31 the latter group.

32

1 The pH monitor chosen for this study was easy to
2 use, acceptable to patients, and recorded pH
3 intramuscularly. It was therefore deemed acceptable
4 for use.

5 6 Results for Example 2

7 The pH and absolute pressure readings during theatre
8 have been plotted on the graph shown in Fig 5, while
9 Fig 7 shows pH results compared with the delta
10 pressure recordings. It is clear that the muscle pH
11 reduced significantly during sustained high ICP, and
12 recovered following fasciotomies.

13 14 Results for Example 3

15 The results can be seen in Figs 6 and 8. The muscle
16 pH remained in the physiological range throughout
17 the operation, while neither the absolute ICP, nor
18 the delta pressure met the current criteria for
19 diagnosing ACS. At no point did the patient show any
20 signs of impending or missed ACS.

21 22 Results for Example 4

23 Sixty one patients admitted to the Orthopaedic
24 Trauma Unit fulfilled the inclusion criteria and
25 agreed to participate in the study. Of this group,
26 pH was successfully recorded in 60 patients.
27 Pressure was also omitted in one patient following
28 damage to one of the probes. Twenty nine (48%)
29 patients have been seen for their six and/or 12
30 month follow up appointments to date.

31

1 The full group was further subdivided into patients
2 who were deemed to have an acute compartment
3 syndrome (ACS), and those who did not (normal) .
4 Patients were included in the ACS group in one of
5 two ways. They were either diagnosed with ACS via
6 clinical assessment and/or pressure measurements by
7 the surgical team, and therefore underwent
8 fasciotomies during their hospital stay, or they
9 were found to have clinical signs of a previous
10 compartment syndrome at subsequent follow up
11 appointments. The median age for each group was
12 similar, and the majority of the patients were male
13 (82%), particularly in the ACS group (94%).
14

15 All three variables, pH, ICP and delta pressure,
16 were recorded for up to 48 hours starting as soon as
17 possible following the patient's injury. The median
18 time from injury to monitor insertion was 11 hours
19 (interquartile range 8.2, 17.7), with a median delay
20 to surgery of 14.5 hours (iq range 7.2, 20). The
21 mean recordings obtained for ICP, dP and pH are
22 displayed in Figs 11 to 13 respectively.
23

24 Figs 11 and 12 show a clear elevation in ICP and a
25 drop in delta pressure (dp) during the first 2 hours
26 of recording. This is followed by a steady, slow
27 recovery over the next 38 hours. Sixty one percent
28 of the whole group suffered a tibial shaft fracture
29 that was treated with IM nailing. This procedure
30 caused high peaks in intra-compartmental pressure,
31 particularly during reaming and nail insertion,

1 which may be at least partly responsible for these
2 initial values.

3

4 The pH (Fig 13) shows a linear pattern of recovery
5 subsequent to an initial drop, and prior to
6 flattening of the curve once normal values are
7 reached (>6.9).

8

9 In order to simplify the analysis of the large
10 quantity of data obtained during this study, the
11 "worst" hourly values of each variable were
12 calculated for each patient. Although this was
13 straightforward for pH measurements, some difficulty
14 was encountered regarding the pressure-based
15 recordings. Those patients who underwent IM nailing
16 experienced many very high peaks in compartment
17 pressure (up to 140mmHg) as a result of reaming and
18 nail insertion, however they were generally not
19 sustained. For some of the readings, the hourly
20 recording fell within the time during the nailing,
21 and therefore the values appear artificially
22 inflated (highest ICP (HICP), lowest dP (LDP)). To
23 compensate for this, moving hourly averages were
24 calculated during IM nailing, to give a better
25 indication of the overall state of the pressure
26 within the compartment (ave. ICP, ave. dP).
27 However, both sets of data were analysed, to ensure
28 that these peaks did not significantly alter the
29 results.

30

1 In order to ensure the accuracy of the recordings
2 obtained throughout each patient's study, both the
3 pH and pressure systems were tested for accuracy
4 upon completion of the study, and therefore any
5 drift that had occurred was detected (see table 3).
6 The drifts in each system were not significantly
7 different between the ACS and normal groups.

8

9 Table 4.1: Drift in systems during monitoring: ICP
10 monitor in air (0), and pH monitor in 7.0 buffer

11

	Full group		ACS		Non ACS		P value
	Median	Iq range	Median	Iq range	Median	Iq range	
ICP	0.00	0, 1.5	0.00	0, 4	0.00	0, 0.75	0.398
pH	7.2	7.025, 7.35	7.1	7.0, 7.35	7.2	7.10, 7.38	0.537

12

13 Intramedullary nailing of the tibia

14 Thirty-seven patients underwent IM nailing of the
15 tibia, with a mean procedure time of 96 minutes (SD
16 21.62).

17

18 During IM nailing, recordings before, during and
19 after each event were recorded. These results were
20 used to produce graphs representative of the average
21 patient in terms of both time and each event (see
22 Figs 14 and 15). These show high peaks in pressure
23 during guidewire insertion, reaming and nail
24 insertion, with a sustained elevation in absolute
25 pressure following nail insertion. The current
26 criteria for ACS (ICP > 30mmHg, delta pressure <
27 30mmHg) are marked on the graphs.

Acute compartment syndrome

For the purposes of this study, the ACS group included all those patients who were diagnosed with ACS during their in-patient stay using clinical parameters and/or pressure studies (n=12). Clinical follow up at 6 and 12 months further identified those with evidence of a previous compartment syndrome (n=4). All patients were then included in one ACS group (n=16).

As with the worst values of ICP, dP and pH, univariate analysis was carried out to determine which factors were associated with the occurrence of ACS. As can be seen from Tables 4.2 and 4.3, none of the demographic or injury related data were associated with an increased risk of developing ACS. Although it appeared initially that the earlier the surgery and monitoring were performed, the more likely the development of ACS, this did not reach statistical significance (Table 4.3).

Table 4.2 Chi-squared tests for categorical patient and injury related factors associated with the development of ACS

	Gender	RTA	Falls	Work	sport	Tibial fract	Side	Open	Grade
Pchi		0.069	0.277				0.741		0.098
Fishers	0.259			0.686	0.686	1.000		0.728	

P values all two-sided

Values are pearsons chi-squared except for those with small numbers in each category which are Fishers exact tests .

Table 4.3: Statistical tests for continuous data related to ACS development

	Age	Delay to Sx	Delay to Mx	Op length
P	0.980	0.063	0.080	0.522*

All represent Mann Whitney tests, except *, which was obtained from t-test

Once more, the worst values of the pH, ICP and dP variables were used for the analysis of the association between these test variables and the development of ACS. The initial values of pH, ICP and delta pressure were also tested to detect any predictive value each had for identifying the subsequent development of an ACS. Table 4.4 shows that both the lowest pH and the highest ICP (both peak and average) recorded were significantly different between the two groups, while the delta pressure difference failed to reach statistical significance. Also of interest was the fact that the initial pH value recorded was also significantly different for the two groups.

Table 4.4: ACS group versus "others" for test variables pH, ICP and dP

Variable	Group	Mean	SD	median	Interquartile range	P
Lowest pH	ACS	6.06	0.19			0.000
	Others	6.49	0.31			
High ICP	ACS			57	35.25; 69.5	0.006
	Others			38	29; 50.75	
Ave ICP	ACS			54	30.5; 58.75	0.041
	Others			32	22.75; 40.75	
Lowest dP	ACS			8.5	0.75; 29.5	0.175
	Others			16.5	10; 30.75	
Ave dP	ACS	17.4		27	12; 36	0.379
	Others	23.3		24	14.25; 34	
Initial pH	ACS	6.48	0.27			0.026
	Others	6.68	0.29			
Initial ICP	ACS			27	17.25; 41.25	0.296
	Others			24	18.75; 29.25	
Initial dP	ACS			29	13; 50.75	0.693
	Others			32	22.75; 48.75	

1 Means and standard deviations are displayed for
2 normally distributed variables and medians and
3 interquartile ranges are noted for variables which
4 are not normally distributed.

5

6 Having found that the initial pH recorded was
7 predictive of the future development of ACS, the
8 group of IM nails were assessed as to the
9 relationship between the pH, ICP and dP values
10 recorded at each event during surgery and the
11 subsequent occurrence of ACS. Although insufficient
12 numbers existed to test the pre- and post-
13 anaesthetic values (n=9), the pH values recorded at
14 each subsequent event were significantly different
15 for each group. Of the pressure variables, only the

1 post-operative delta pressure was significantly
2 different between the two groups (see table 4.5).

3

4 Table 4.5: ACS vs normal: Parameters monitored
5 during events of IM nailing with p values (mann
6 whitney)

7 * significant to the 0.05 Level (two-tailed)

8 ** significant to the 0.01 level (two-tailed)

9

	PH			ICP (mmHg)			Delta Pressure (mmHg)		
	ACS	Non	p	ACS	non	p	ACS	non	P
T	6.5	6.7	0.051	29	24	0.338	28	28	0.560
GW	6.5	6.6	0.052	56.5	45	0.231	1	14.5	0.377
R	6.3 5	6.6	0.023*	67	48	0.224	-10	9.5	0.203
N	6.3 5	6.6	0.006* *	77.5	59	0.108	-11.5	4	0.340
TR	6.3	6.8	0.003* *	45.5	25.5	0.185	34	28	0.762
REC	6.3	6.7	0.001* *	33	26.5	0.560	27.5	46	0.023*

10

11

12 Figs 16 and 17 are graphs of absolute ICP and pH
13 respectively during Intramedullary nailing. The
14 diamonds represent the ACS group and the squares
15 represent the ACS group.

16

17 Recovery following fasciotomies

18 Twelve patients underwent fasciotomies during this
19 study. Data was collected throughout the procedure,
20 and each variable was recorded at specific time

1 points: Prior to fasciotomies, and following each
2 dermatomy, and each fasciotomy. The data obtained is
3 displayed in Fig 18. The diamonds represent pH and
4 the squares represent pressure. Both pH and
5 pressure recovered during the surgery, however,
6 although the pressure had significantly reduced
7 following the last fasciotomy ($p=0.008$), the pH had
8 not recovered significantly by this time point
9 ($p=0.284$).

11 Intra-Compartmental Pressure vs pH

12 In order to further compare the diagnostic strength
13 of pressure based variables with pH in relation to
14 ACS, the initial full group graphs were split into
15 those with, and those without signs of ACS. In
16 addition, the sensitivity and specificity for each
17 level of each variable was calculated, and ROC
18 curves produced. Finally, further univariate
19 analysis was carried out using the best levels of
20 each variable identified via the previous tests.

22 The data for ICP, delta pressure and pH over the
23 first 40 hours are presented in Figs 19 to 21
24 respectively. For pressure related data, the only
25 values which were significantly different between
26 the groups occurred at the 1 and 2 hour points for
27 ICP ($p=0.043$; $p=0.000$), and only at the 2 hour point
28 for dP ($p=0.000$). However, the pH values recorded
29 for the ACS group were significantly different from
30 those without the syndrome for each time point up to
31 33 hours. This shows that pH readings can provide a

1 better indication of acute compartment syndrome than
2 ICP readings. Furthermore, the slope of the line is
3 similar in the recovery period.

4

5 Correlations were performed comparing the three
6 variables being tested to determine any relationship
7 that existed between pH and pressure based
8 recordings; the results are shown in Table 4.6. As
9 expected, the ICP and dP values were highly
10 correlated (dP=diastolic blood pressure - ICP), and
11 the initial pH values correlated well with the
12 lowest pH values subsequently recorded. However,
13 neither the lowest pH nor the initial pH values
14 obtained were correlated with either pressure
15 measurement.

16

17 Table 4.6: Correlations between ICP, dP, and pH
18 values recorded

19

	Low pH	High ICP	Low dP	Initial pH	Initial ICP	Initial dP
Low pH		0.560	0.549	0.000*	0.830	0.495
High ICP	0.560		0.000*	0.489	0.000*	0.005*
Low dP	0.549	0.000*		0.153	0.000*	0.000*
Initial pH	0.000*	0.489	0.153		0.714	0.196
Initial ICP	0.830	0.000*	0.000*	0.714		0.000*
Initial dP	0.495	0.005*	0.000*	0.196	0.000*	

20 All correlations are Spearman's rho, except those
21 comparing pH values (Pearson's correlations)

22 * correlation significant to the 0.01 level (two-
23 tailed)

1 The sensitivity and specificity for pH, ICP and
2 delta pressure were calculated, allowing ROC curves
3 to be produced (Figs 22 to 24 respectively).

4 Area under curves:

5 lowest pH: 0.875

6 Highest ICP: 0.732

7 average high ICP: 0.673

8 Lowest dP: 0.591

9 average low dP: 0.577

10

11 Given the significance of the initial pH value at
12 predicting ACS, the sensitivity and specificity were
13 also calculated for ICP, delta pressure and pH, and
14 the results are displayed in Figs 25 to 27
15 respectively.

16

17 Areas under curve:

18 ICP: 0.589

19 DP: 0.540

20 PH: 0.681

21

22 By examining the sensitivity and specificity for
23 each variable from the ROC curves generated, the
24 best levels at which to diagnose ACS for each
25 variable were determined. This was less than 6.4
26 for pH (93% sensitivity, 68% specificity), greater
27 than 40mmHg for ICP (69% sensitivity, 66%
28 specificity) and less than 20mmHg for delta pressure
29 (53% sensitivity, 64% specificity). Chi-squared
30 tests were then used for each variable, and only the

critical pH and ICP levels identified were associated with development of the syndrome (table 4.7). Chi squared tests were also carried out on the most commonly used pressure-based criteria for ACS currently (table 4.8).

Table 4.7: Chi-squared tests for best fit predictive measurements associated with the development of ACS (pearsons chi)

	pH<6.4	ICP>40	DP<20
Pchi	0.000	0.039	0.167

Table 4.9: Chi-squared tests for predictive value of currently used levels of ICP and dP

	ICP>30	ICP>40	ICP>50	DP<30
Pchi	0.195	0.039	0.002	0.481*

Values are pearsons chi, except * fishers exact test

Results for Example 5

pH

The first point of attack of ischaemia is the cell's aerobic respiration, i.e. oxidative phosphorylation by the mitochondria. As the oxygen tension within the cell decreases there is a loss of oxidative phosphorylation and decreased generation of ATP.

This switch to anaerobic metabolism results in an increased rate of glycolysis designed to maintain the cells energy sources by generating ATP through the metabolism of glucose derived from glycogen. As a consequence glycogen stores are rapidly depleted, resulting in the accumulation of lactic acid and inorganic phosphates from the hydrolysis of

1 phosphate esters. This reduces the intracellular
2 and interstitial pH.

3

4 Table 5.1 displays the decrease in muscle pH in
5 relation to ischaemic time.

Time (min)	pH	SD
0	7.14	0.05
2	6.95	0.05
4	6.84	0.07
6	6.76	0.09
8	6.70	0.10
10	6.65	0.11
15	6.57	0.11
30	6.44	0.08
45	6.35	0.07
60	6.31	0.08
75	6.29	0.09
90	6.26	0.07
105	6.24	0.05
120	6.22	0.04
135	6.21	0.04
150	6.18	0.04

6

7 Although tissue oxygen levels are depleted rapidly
8 after the onset of muscle ischaemia, tissue pH
9 continues to decline over a prolonged period under
10 similar conditions. This is clearly visible in
11 figure 28.

12

13 Glucose 6 Phosphate

14 Glucose 6 phosphate (G6P) acts as a key crossroads
15 governing the metabolism. Glucose entering the cell
16 can rapidly be phosphorylated to G6P, which can be
17 stored as glycogen, degraded by way of pyruvate, or
18 converted into ribose 5 phosphate.

19

20 Under "normal conditions", G6P can be formed by the
21 mobilization of glycogen, or it can be synthesised

1 from pyruvate or glycogenic amino acids by the
2 gluconeogenic pathway. However during ischaemia and
3 anaerobic metabolism, Glucose 6 phosphate acts as a
4 crossroads feeding the glucose molecules into the
5 glycolytic pathway, in an attempt to maintain ATP
6 levels.

7

pH	[G6P]	SD
7.1	1.89	0.29
7	1.77	0.24
6.9	1.45	0.39
6.8	1.36	0.35
6.7	0.78	0.12
6.6	0.76	0.09
6.5	0.57	0.07
6.4	0.52	0.06
6.3	0.48	0.12
6.2	0.39	0.04

8 Table 5.2

9
10 Both Table 5.2 and Figure 29 clearly demonstrate the
11 rapid fall of G6P with the onset and progression of
12 ischaemia.

13 Lactate

14 Under anaerobic conditions, the reduction of
15 pyruvate to lactate consumes NADH and regenerates
16 NAD⁺ that is essential for continued glycolysis.

17
18
19 The reduction of pyruvate is catalysed by Lactate
20 Dehydrogenase, which forms the L isomer of lactic
21 acid. The overall equilibrium of this reaction
22 strongly favours lactate formation and once formed,
23 lactate can only be reconverted to pyruvate in the
24 liver. Hence, within the muscle, lactate is a
25 metabolic dead end.

pH	[Lactate]	SD
7.1	17.67	8.50
7	31.00	9.93
6.9	46.71	7.30
6.8	51.33	4.63
6.7	64.80	8.93
6.6	82.50	11.12
6.5	95.67	7.50
6.4	127.00	5.00
6.3	140.67	15.37
6.2	164.67	9.29

Table 5.3

Both Table 5.3 and Figure 30 clearly demonstrate the gradual elevation of Lactate within the muscle tissue, with the progression of ischaemia.

We know that the pathophysiology of ACS results in inadequate tissue oxygen delivery, precipitating anaerobic metabolism. However in addition ACS impairs the removal of the products of anaerobic glycolysis, and one might hypothesise that this may result in an increased accumulation of lactic acid.

Pyruvate

Pyruvate, the product of glycolysis, represents an important junction point in carbohydrate metabolism. The initial steps of glycolysis or glycogenolysis are anaerobic and are the predominant metabolic pathways of energy production for preservation of cell integrity in ischaemic skeletal muscle.

The reactions of glycolysis occur in the cytoplasm of the cell, and the pyruvate formed is not phosphorylated and is, therefore, free to leave the

cell. Some pyruvate will escape from tissues such as muscle when the rate of glycolysis is high, but most is further metabolised. Pyruvate produced by glycolysis during ischaemia is ultimately metabolised under anaerobic conditions to form lactate.

pH	[Pyruvate]	SD
7.1	1.60	0.27
7	1.58	0.25
6.9	1.50	0.41
6.8	1.20	0.22
6.7	0.96	0.33
6.6	0.62	0.20
6.5	0.56	0.22
6.4	0.46	0.21
6.3	0.46	0.17
6.2	0.26	0.09

Table 5.4

Table 5.4 and Figure 31 demonstrate the fall of tissue Pyruvate concentrations. These closely mirror the similar fall in G6P concentrations, which support the gradual utilisation of the glycolytic metabolites with ensuing ischaemia.

pH Verification

Previous studies performed by Sahlin et al found a close relationship between pH and the concentrations of lactate and pyruvate in skeletal muscle at rest and following various levels of circulatory occlusion.

$$\text{pH} = -0.00532(\text{lactate} + \text{pyruvate}) + 7.06$$

1 This enables us to verify the pH measurements of the
 2 intramuscular probe with a calculated pH, derived
 3 from the above assay results.

4
 5 The Intramuscular pH measurements and corresponding
 6 lactate concentration, pyruvate concentration and
 7 calculated pH are demonstrated in table 5.5.

8

Specimen No	IM pH measurement	[Lactate] mmol/kg	[Pyruvate] mmol/kg	Calc. pH measurement
1.00	6.90	46.00	1.73	6.81
2.00	6.80	51.00	0.86	6.78
3.00	6.70	55.00	1.69	6.76
4.00	6.90	49.00	1.79	6.79
5.00	6.80	55.00	1.49	6.76
6.00	6.70	60.00	1.17	6.73
7.00	6.50	98.00	0.91	6.53
8.00	6.90	43.00	0.69	6.83
9.00	6.70	59.00	0.52	6.74
10.00	6.70	76.00	0.67	6.65
11.00	6.60	86.00	0.46	6.60
12.00	6.80	45.00	1.14	6.81
13.00	6.70	55.00	0.84	6.76
14.00	6.60	70.00	0.49	6.68
15.00	6.50	85.00	0.37	6.61
16.00	6.90	44.00	1.75	6.82
17.00	6.80	57.00	1.39	6.75
18.00	6.70	58.00	1.16	6.75
19.00	6.70	64.00	0.85	6.71
20.00	6.60	78.00	0.62	6.64
21.00	6.90	43.00	1.49	6.82
22.00	7.00	31.00	1.89	6.89
23.00	6.50	90.00	0.35	6.58
24.00	6.20	175.00	0.21	6.13
26.00	7.10	26.00	1.90	6.91
27.00	6.90	40.00	1.79	6.84
28.00	6.60	96.00	0.90	6.54
29.00	6.40	132.00	0.69	6.35
30.00	6.30	148.00	0.59	6.27
31.00	6.30	151.00	0.51	6.25
32.00	6.20	162.00	0.36	6.20
33.00	7.00	45.00	1.66	6.81
34.00	6.90	62.00	1.28	6.72
35.00	6.70	79.00	0.74	6.64
36.00	6.50	94.00	0.70	6.56

37.00	6.30	123.00	0.27	6.40
38.00	6.20	157.00	0.20	6.22
39.00	7.10	9.00	1.36	7.00
40.00	7.00	23.00	1.38	6.93
41.00	6.80	47.00	1.11	6.80
42.00	6.70	68.00	0.99	6.69
43.00	6.50	105.00	0.60	6.50
44.00	6.40	122.00	0.43	6.41
45.00	7.10	18.00	1.55	6.96
46.00	7.00	25.00	1.37	6.92
47.00	6.80	53.00	1.19	6.77
48.00	6.70	74.00	0.98	6.66
49.00	6.50	102.00	0.41	6.52
50.00	6.40	127.00	0.27	6.38

Table 5.5

A simple plot of the results of Intramuscular vs. Calculated pH (Figure 32) demonstrate the results lying near the line of equality, the line on which all points would lie if the two measurements were exactly the same, every time. The Trend line of these points gave an equation $y = 1.1196x - 0.7701$ with an $R^2 = 0.9265$. The high correlation of the results shows that the pH probe is providing consistent and reliable results.

To assess where any bias lies between the Intramuscular and Calculated pH measurements, a Measurement of Agreement curve was constructed (Figure 33), comparing the average of the corresponding pHs to the difference between the corresponding pHs. This demonstrated the greatest bias lies at the upper pH levels of 7.1 to 6.8, which actually corresponds to the physiological range of muscle ischaemia.

1 ATP and PCr

2 Within the cells, reactions which are not
3 thermodynamically favoured may nevertheless be
4 driven if coupled to reactions that have large,
5 negative free energy changes. In living systems,
6 the hydrolysis of certain phosphate compounds is
7 frequently used in such coupling. The phosphate
8 transfer potential ranks these compounds according
9 to their ability to phosphorylate other compounds
10 under standard conditions. Adenosine Triphosphate
11 (ATP) lies about midway on the scale of phosphate
12 transfer potential. This position is a strategic
13 one, for ATP serves as the general "free energy
14 currency" for virtually all cellular processes and
15 is essential for the maintenance cell function and
16 integrity.

17

18 There are several metabolites with greater phosphate
19 transfer potentials than ATP. Phosphocreatine,
20 otherwise known as creatine phosphate, is such a
21 compound. It is abundant in skeletal muscle, with
22 quantities 4 times that of ATP. There it acts as a
23 shuttle and a reservoir of the phosphate bond energy
24 from the ATP in the mitochondria to the myofibrils,
25 where its energy is transduced to the mechanical
26 energy of muscle contraction.

27

28 Tables 5.6 and 5.7 display the fall off both ATP and
29 PCr with decreasing pH. These are further
30 demonstrated on Figures 34 and 35.

31

32

pH	[ATP]	SD
7.10	22.82	1.35
7.00	19.52	0.53
6.90	15.31	2.36
6.80	12.73	2.38
6.70	9.81	1.40
6.60	6.96	1.56
6.50	4.83	0.64
6.40	3.23	1.31
6.30	2.32	1.54
6.20	2.99	2.12

1 Table 5.6

2

pH	[PCr]	SD
7.10	114.03	26.53
7.00	117.09	33.94
6.90	85.40	30.07
6.80	42.82	11.46
6.70	35.59	11.12
6.60	20.63	2.47
6.50	18.12	5.57
6.40	10.89	3.55
6.30	11.29	0.87
6.20	11.40	12.68

3 Table 5.7

4

5 As ischaemia commences, the oxygen tension within
6 the cell decreases and there is a loss of oxidative
7 phosphorylation and decreased generation of ATP. At
8 this point, the metabolic demand of the cell can no
9 longer be met via aerobic metabolism and anaerobic
10 processes begin in earnest. The switch to anaerobic
11 metabolism results in an increased rate of
12 glycolysis designed to maintain the cell's energy
13 sources by generating ATP through the metabolism of
14 glucose derived from glycogen. However with
15 increased duration of ischaemia these reserves are
16 utilised with resulting depletion of ATP. This
17 depletion of ATP has widespread effects on many
18 systems of the cell. If ischaemia persists,

1 irreversible injury ensues and ischaemic tissue
2 death ultimately occurs. This process has
3 morphological hallmarks, but the biochemical
4 explanation for the critical transition from the
5 reversible injury to cell death has remained
6 elusive.

7
8 However, two phenomena consistently characterise
9 irreversibility. The first is the inability to
10 reverse mitochondrial dysfunction causing marked ATP
11 depletion; the second is the development of profound
12 disturbances in membrane function. ATP depletion
13 clearly contributes to the functional and structural
14 consequences of ischaemia, and may also lead to
15 membrane damage.

16
17 It is difficult to assess to what level ATP must
18 drop, before irreversible ischaemia is obtained.
19 Certainly previous research⁷ found that ATP levels
20 can drop to nearly 50% in chronic disease states,
21 without morphological irreversible ischaemic
22 changes, while an ATP decline to less than 40% were
23 found in patients with end stage Multi-organ failure
24 who later died. If we were therefore to extrapolate
25 the results above and use 40% as a level consistent
26 with irreversible ischaemia, this would correspond
27 to an ATP concentration of 9-12mmol/kg dw,
28 equivalent to an intramuscular pH of approximately
29 6.65.

30
31 Thus, the pH results from the biopsy can be used to
32 verify the accuracy of the pH readings from the pH

1 monitor in the muscle tissue, and the damage
2 sustained by skeletal muscle can be correlated with
3 specific levels of ICP and pH.

4
5 Results for Example 6

6 The aim of this study was to demonstrate the ability
7 to monitor the muscle pH changes associated with
8 limb ischaemia, in both the acute and chronic forms.
9 In vascular surgery there are a number of novel uses
10 for pH monitoring including assisting in the
11 decision to re-vascularise compromised limbs or to
12 primarily amputate to avoid the potentially life
13 threatening systemic effects of re-vascularisation.

14
15 The calibration, sterilisation and insertion
16 techniques used in this study were identical to
17 those used earlier. Markers were used in this
18 instance during surgery for clamping off the artery
19 (ON), release of the clamp (OFF), return to full
20 circulation (CIRC) and in some cases, during the
21 angiogram (ANGIO) used to check graft patency.

22
23 Twelve patients fulfilled the ethical entry criteria
24 and agreed to participate in the study. Of these
25 66% were male, and the mean age was 69 years. 33%
26 were acute on chronic ischaemic limbs, the remainder
27 were chronic cases. All underwent bypass procedures
28 from the femoral artery to either the popliteal
29 artery or distal vessels. Examples of the typical
30 recordings of muscle pH gained are presented in
31 figures 36, 37 and 38. The chronic ischaemic limbs
32 start within a normal physiological range of pH (6.9

1 - 7.2) and this decreases during surgery. On the
2 other hand the patients with acute ischaemic events
3 compounded by chronic limb ischaemic have a low
4 muscle pH prior to bypass graft surgery, but in time
5 this recovers as a result of recommencing the muscle
6 circulation.

7
8 As with the previous examples, low muscle pH was
9 associated with the symptoms and signs of muscle and
10 nerve compromise. In the acutely ischaemic limbs,
11 which started at pH of less than 6.4, each patient
12 had numbness in their foot and weakness of foot
13 dorsiflexion.

14
15 Patient X: Acute on chronic limb ischaemia
16 An angiogram pre-operatively showed no blood supply
17 going to the anterior compartment of the leg. He
18 had weakness of dorsiflexion of the foot and great
19 toe, and reduced sensation on the dorsum and sole of
20 his foot. A starting pH of 5.8 indicates severe
21 circulatory compromise in the anterior compartment.
22 Following re-vascularisation, some immediate
23 recovery is evident following removal of the
24 vascular clamp (graph), but this recovery continued
25 for the next 24 hours (graph). He continued to have
26 signs of muscle and nerve damage following the
27 recording period, but a degree of improvement was
28 evident prior to terminating the muscle pH
29 recording.

30

31 Patient Y: Chronic limb ischaemia

1 This lady had chronic ischaemia only, with
2 collateral circulation present on angiogram pre-
3 operatively. Throughout surgery, with the muscle in
4 a resting state, the muscle pH remained within a
5 normal physiological range (6.9-7.2). Despite
6 clamping of the major blood vessel to the anterior
7 compartment, little change was noted in the muscle
8 pH (graph). This would suggest that the collateral
9 circulation present was sufficient to maintain
10 aerobic metabolism in muscle in a resting state. At
11 no point during recording did the patient show signs
12 of muscle or nerve compromise.

13
14 Modifications and improvements can be made without
15 departing from the scope of the invention. For
16 example, it is not necessary to use the pressure
17 and pH monitors described here; other similar
18 devices could be used.

19
20 The following disclosures referred to above are
21 incorporated herein by reference:

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18 Determined in Biopsy Samples of *Musculus Quadriceps*
19 *Femoris* of Man at Rest. *Methods and Variance of*
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22 8 Olsen, C. An Enzymatic Fluorimetric Micromethod
23 for the Determination of Acetoacetate, B-
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25 *Acta.* 33, 293-300, 1971
26
27
28
29
30
31
32

1 Claims

- 2
- 3 1. A method of determining the presence or
4 severity of ischaemia in a tissue, the method
5 comprising the steps of inserting a pH sensor
6 into the tissue, and measuring the
7 intracompartmental pH in the tissue.
8
- 9 2. A method as claimed in claim 1, wherein the
10 tissue is muscle.
11
- 12 3. A method as claimed in any preceding claim,
13 wherein a second probe is used to measure the
14 intracompartmental pressure in the tissue.
15
- 16 4. A method as claimed in any preceding claim,
17 wherein the or each sensor is mounted on a
18 respective catheter.
19
- 20 5. A method as claimed in any preceding claim,
21 wherein the or each catheter is inserted into
22 the muscle through a respective cannula.
23
- 24 6. A method as claimed in any preceding claim,
25 wherein the or each cannula is inserted into
26 skeletal muscle in an orientation that is
27 generally parallel to the muscle fibres.
28
- 29 7. A method as claimed in any preceding claim,
30 wherein the tissue is adjacent to a bone
31 fracture, and wherein the or each cannula is

1 inserted into the muscle adjacent to, but not
2 communicating with, the fracture site.
3

4 8. A method as claimed in any preceding claim,
5 wherein the reading from the or each sensor is
6 compared with a calibrated scale to determine
7 the extent of tissue damage.
8

9 9. A method as claimed in any preceding claim,
10 wherein the ischaemia involves Acute
11 Compartment Syndrome.
12

13 10. A method as claimed in any preceding claim,
14 wherein the ischaemia involves a transplant or
15 tissue flap.
16

17 11. A method as claimed in any preceding claim,
18 wherein the ischaemia involves septic shock,
19 neurogenic shock, cardiogenic shock or
20 hypovolaemic shock.
21

22 12. A method as claimed in any preceding claim,
23 wherein the ischaemia involves vascular
24 surgery.
25

26 13. Apparatus for determining the presence or
27 severity of ischaemia, the apparatus having a
28 pH sensor adapted to be inserted into a muscle.
29

30 14. Apparatus as claimed in claim 13, wherein the
31 pH sensor is mounted on a catheter.
32

- 1 15. Apparatus as claimed in claim 14, wherein the
2 catheter is glass-tipped.
3
- 4 16. Apparatus as claimed in claim 14, wherein the
5 catheter is antimony-tipped.
6
- 7 17. Apparatus as claimed in any one of claims 12-
8 16, wherein the apparatus also includes a
9 pressure sensor coupled to a pressure recording
10 device.
11
- 12 18. Apparatus as claimed in claim 17, wherein the
13 pH sensor and the pressure sensor are mounted
14 on the same catheter.
15
- 16 19. Apparatus as claimed in any one of claims 12-
17 18, wherein the pH sensor is connected to a pH
18 recorder.
19
- 20 20. The use of a pH sensor device for the
21 determination of the presence or the severity
22 of ischaemia and typically Acute Compartment
23 Syndrome.
24
- 25 21. The use of a pH sensor device according to
26 claim 20, wherein the ischaemia involves Acute
27 Compartment Syndrome.
28
- 29 22. A method of determining information concerning
30 the condition of soft tissue, the method
31 comprising the steps of inserting a pH sensor

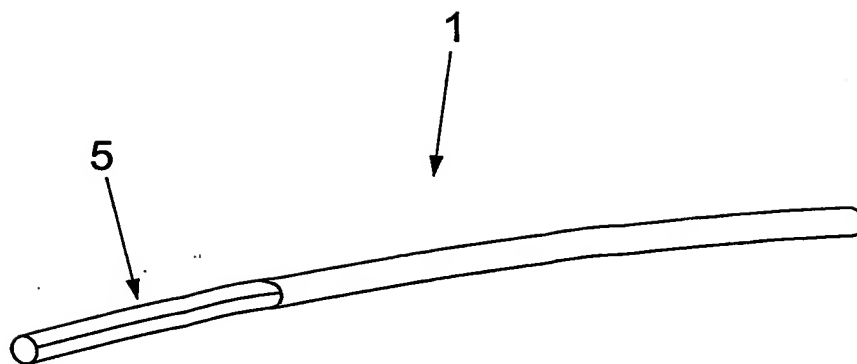
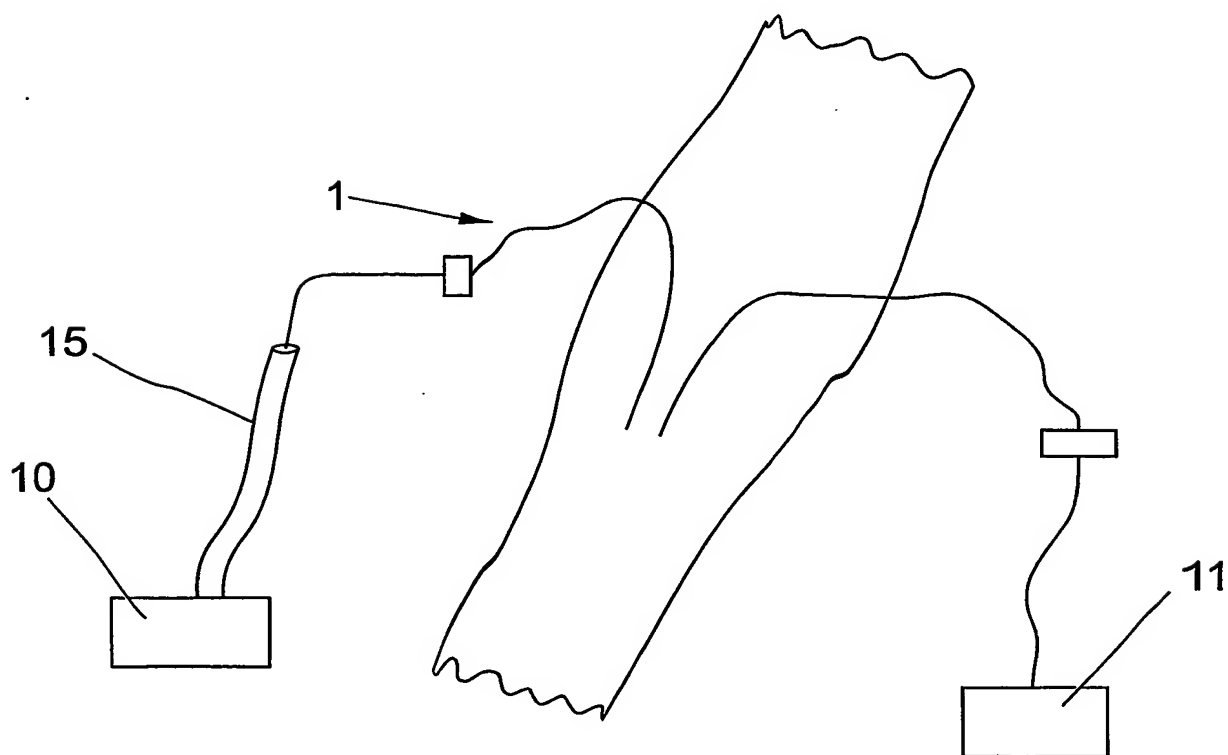
1 into the soft tissue and measuring the pH in
2 the tissue.

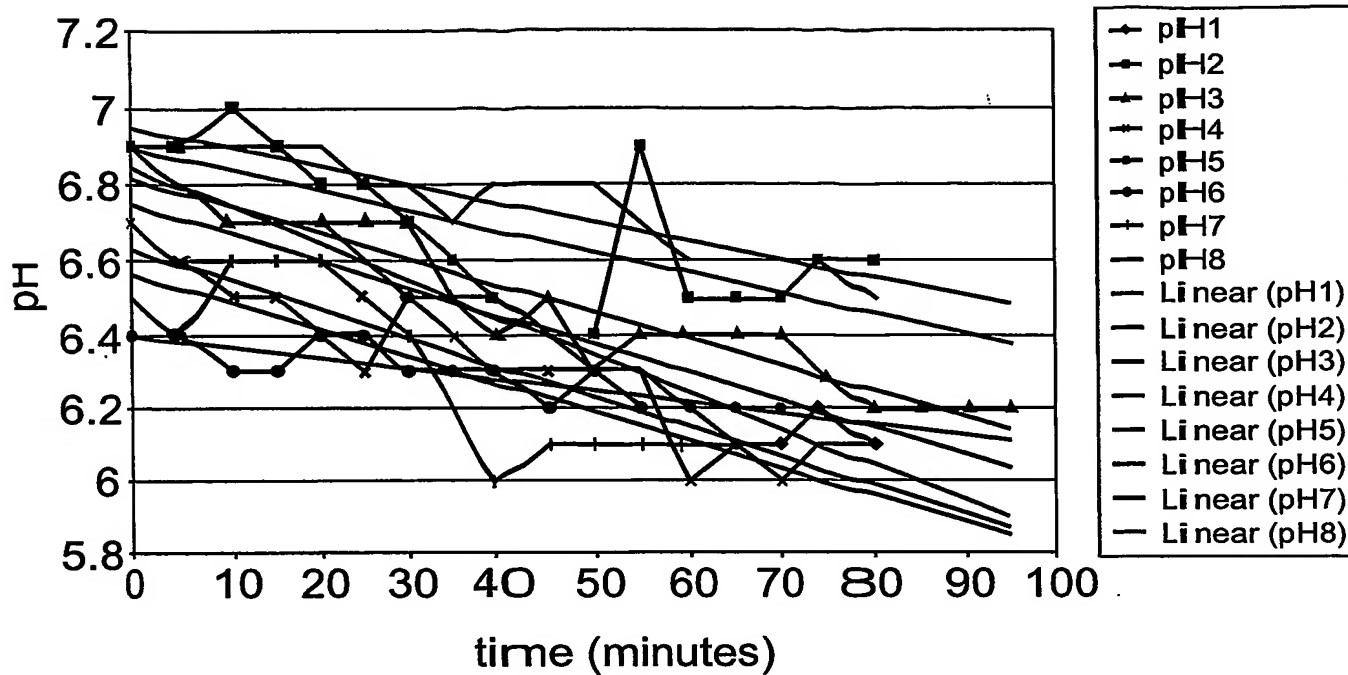
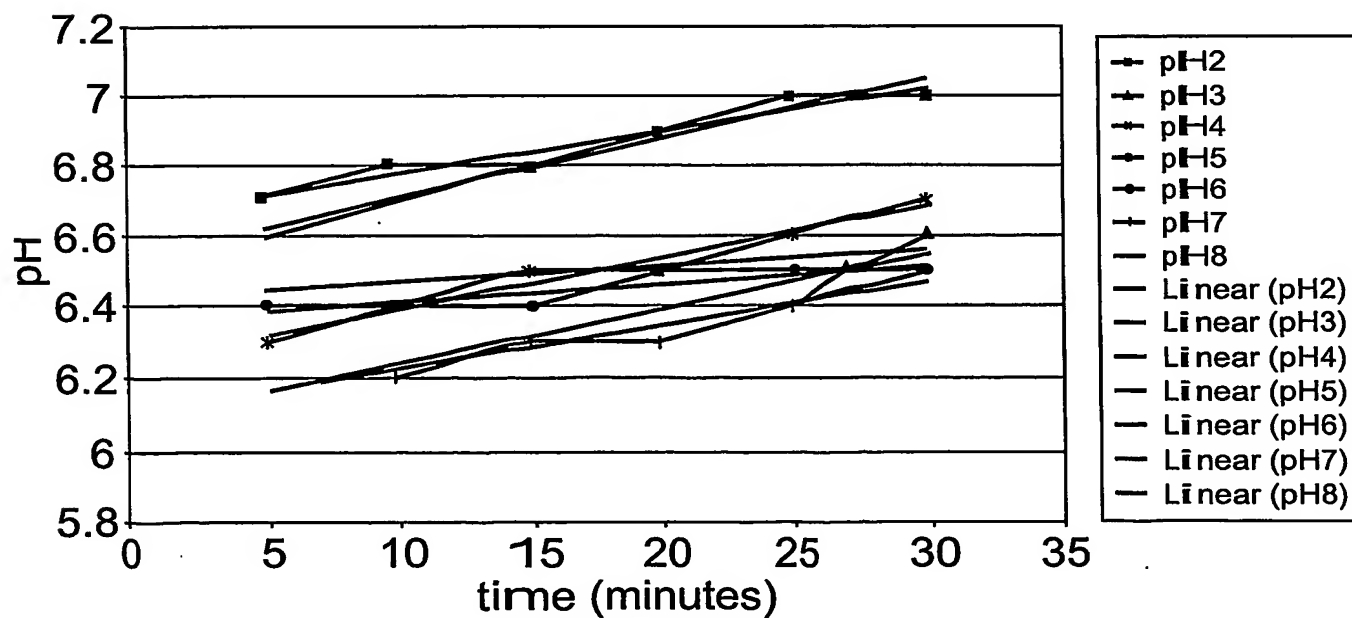
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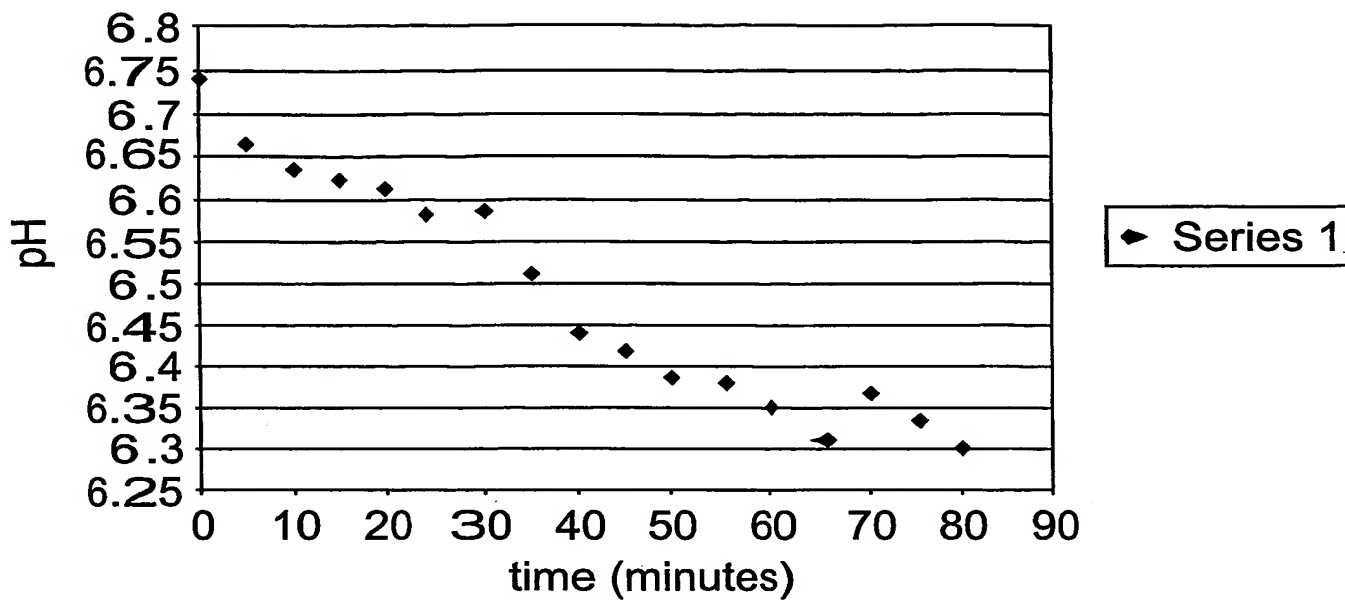
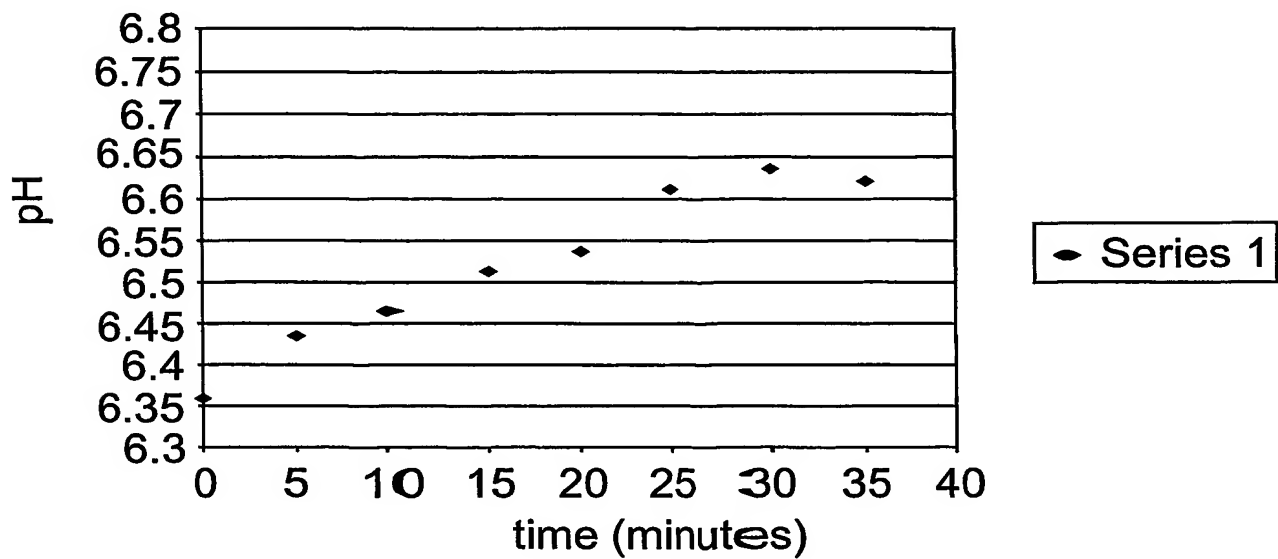
4 23. A method of measuring intracompartamental pH,
5 including the step of inserting a pH sensor
6 directly into a muscle.

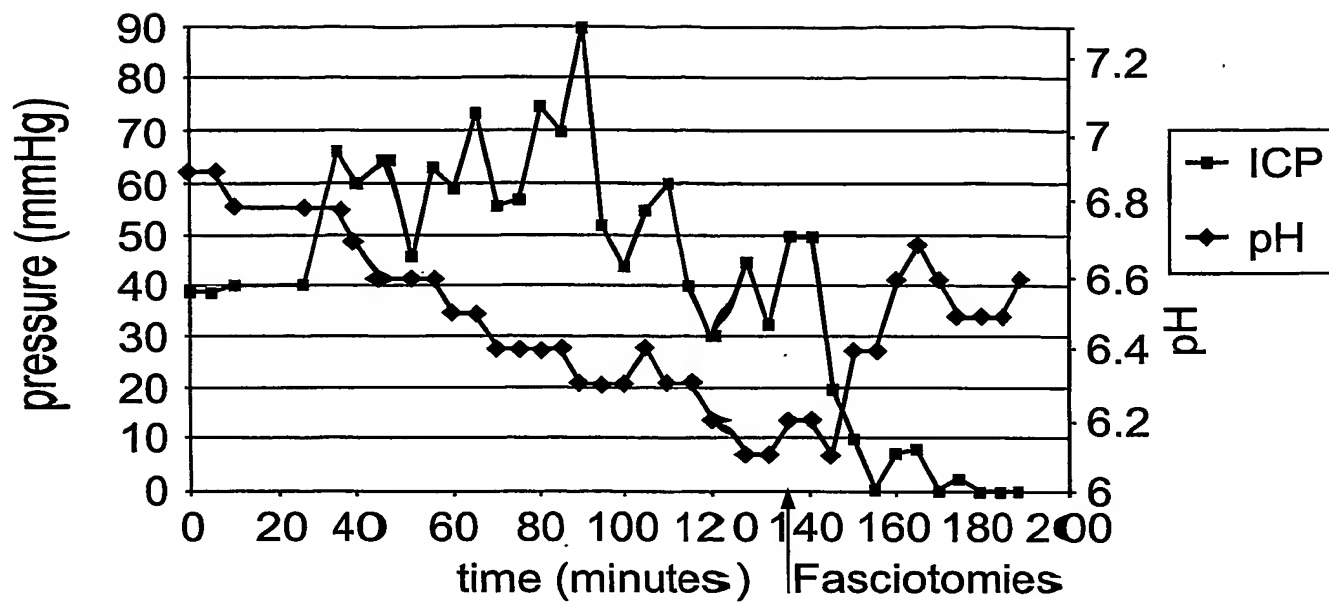
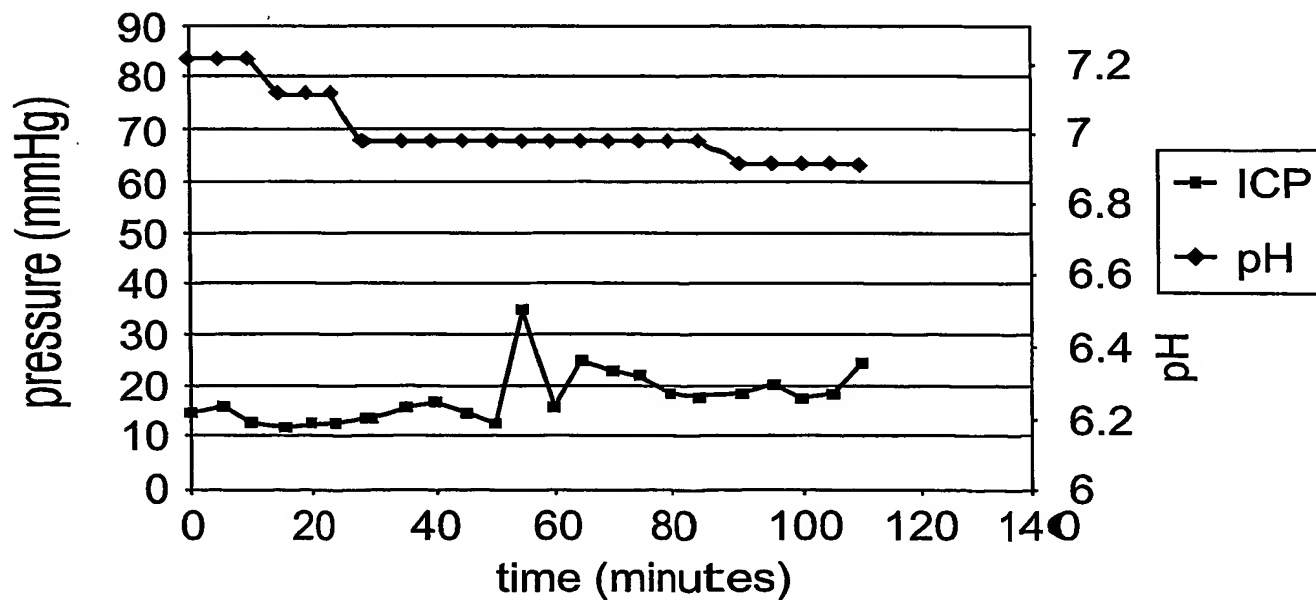
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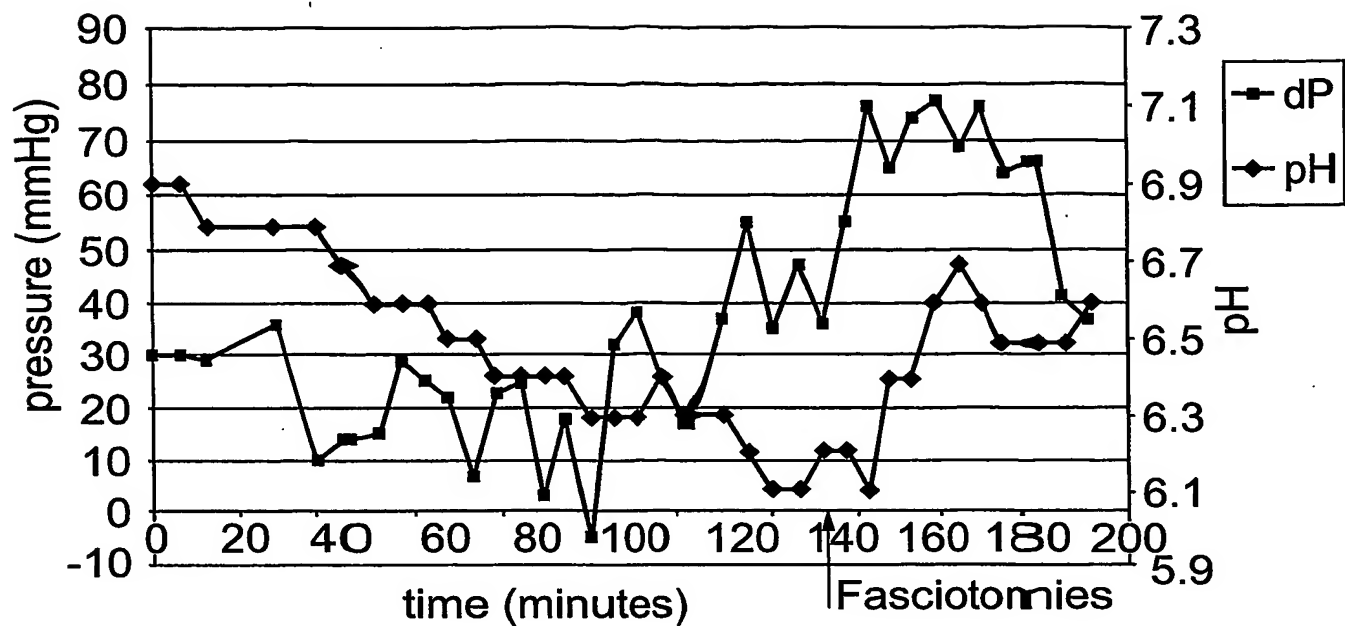
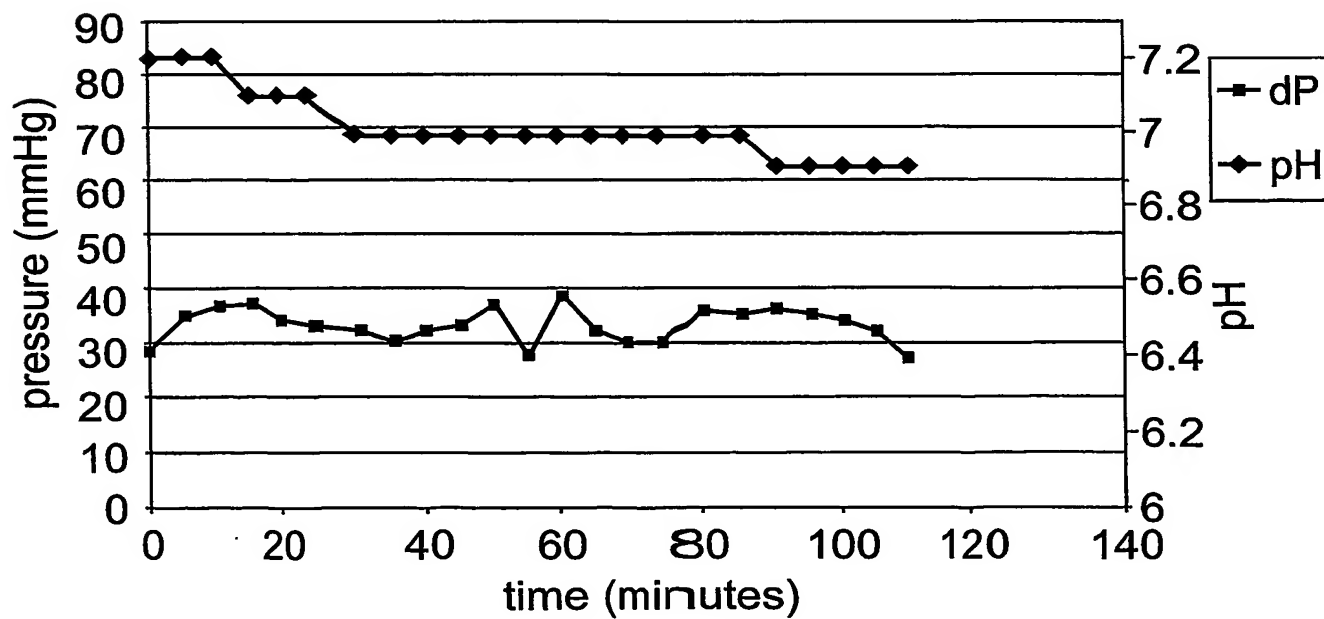
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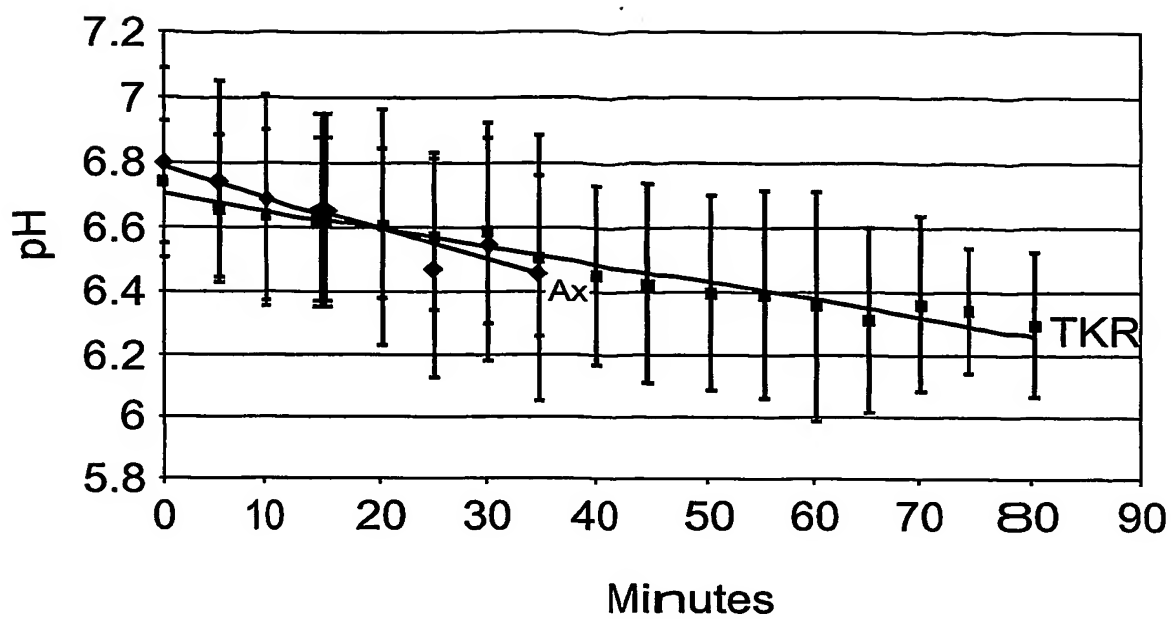
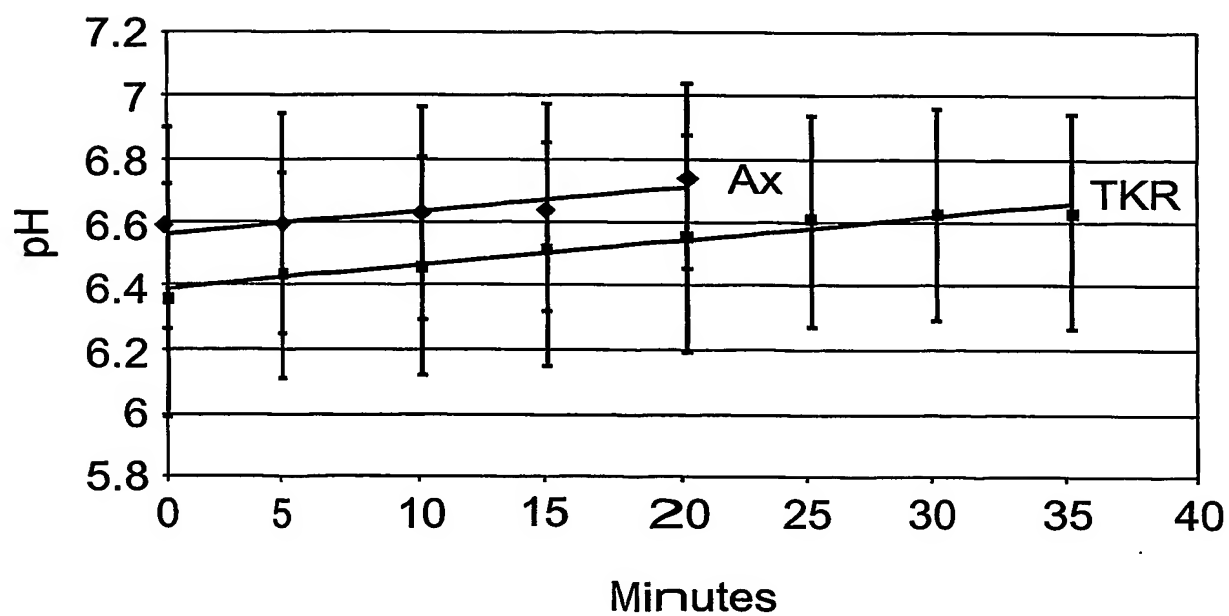
*Fig. 1**Fig. 2*

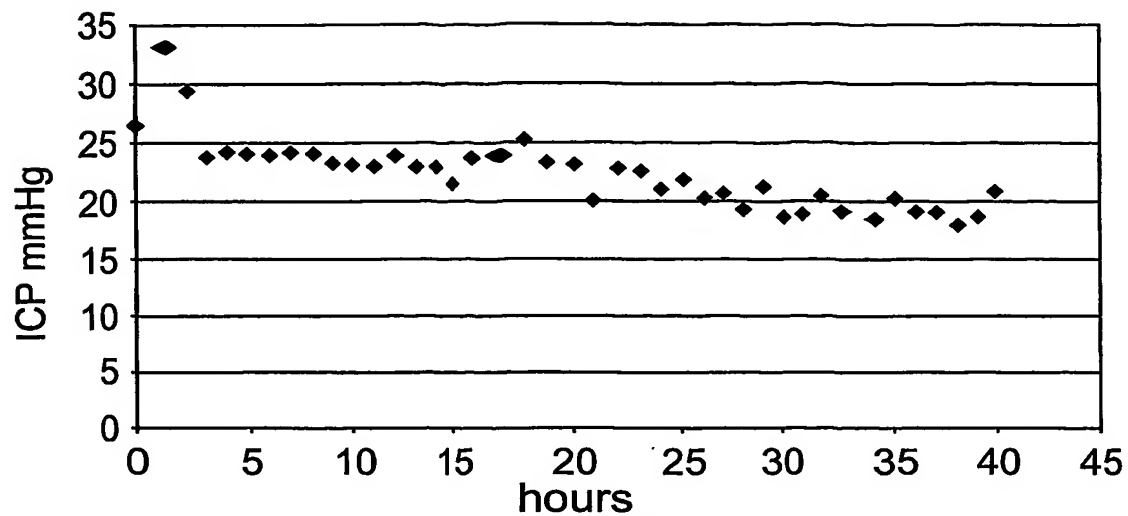
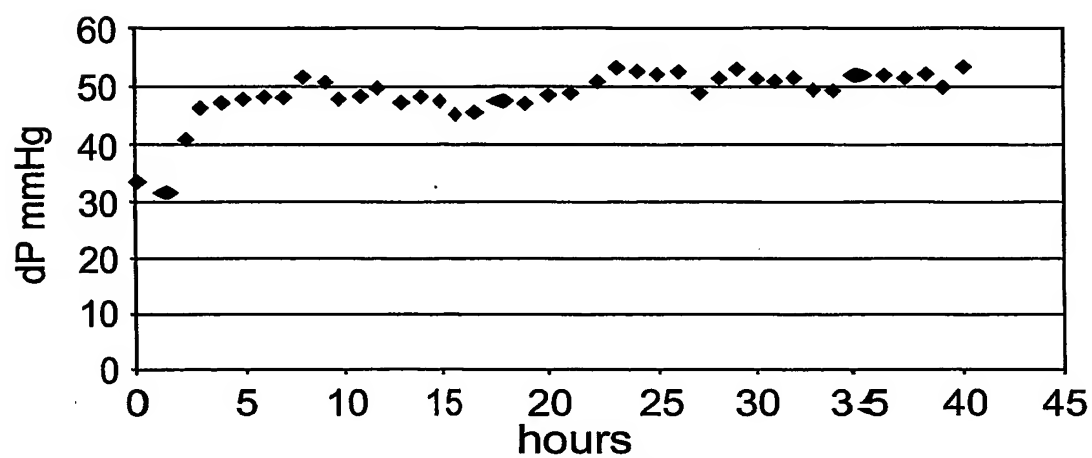
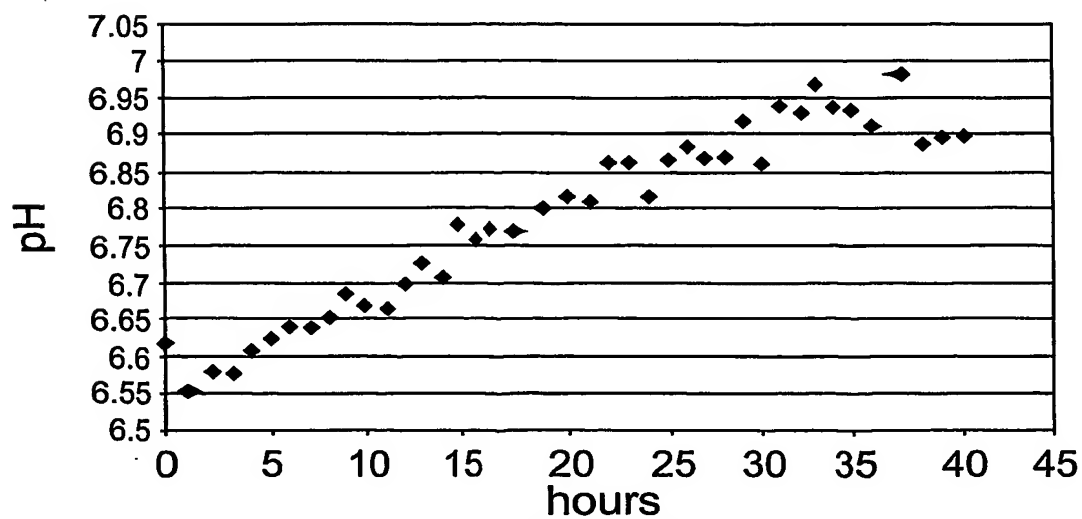
*Fig. 3a**Fig. 4a*

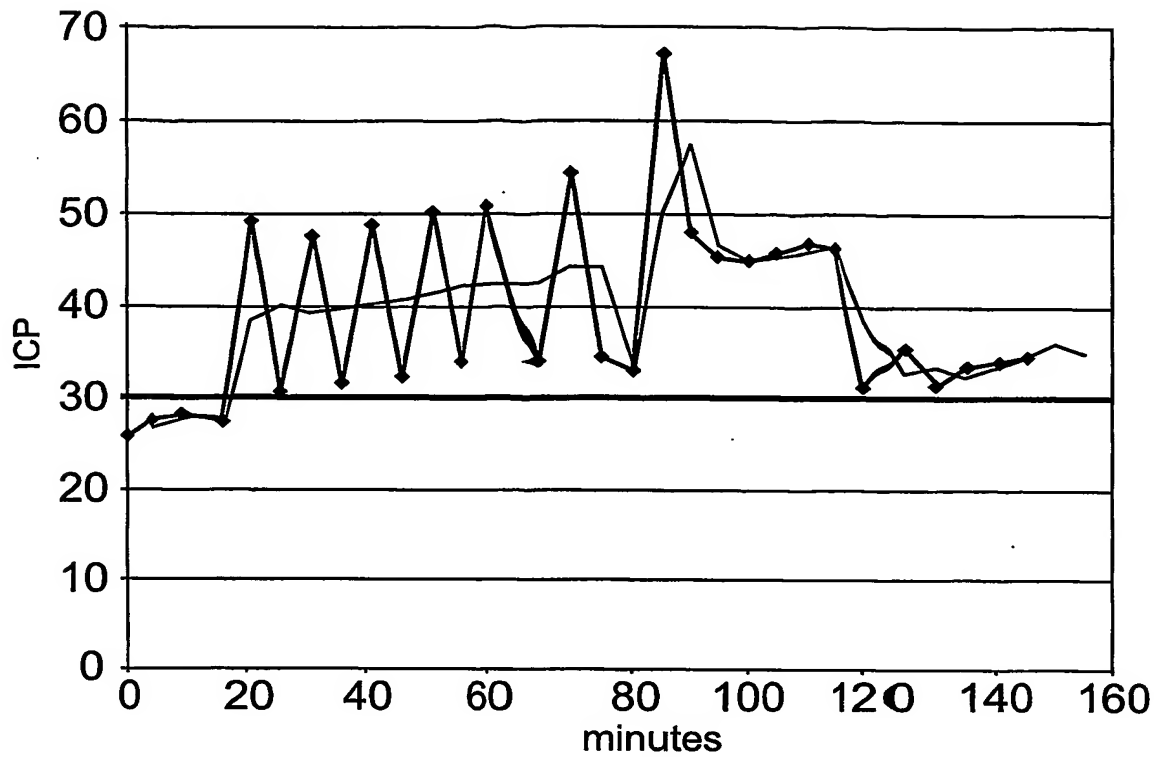
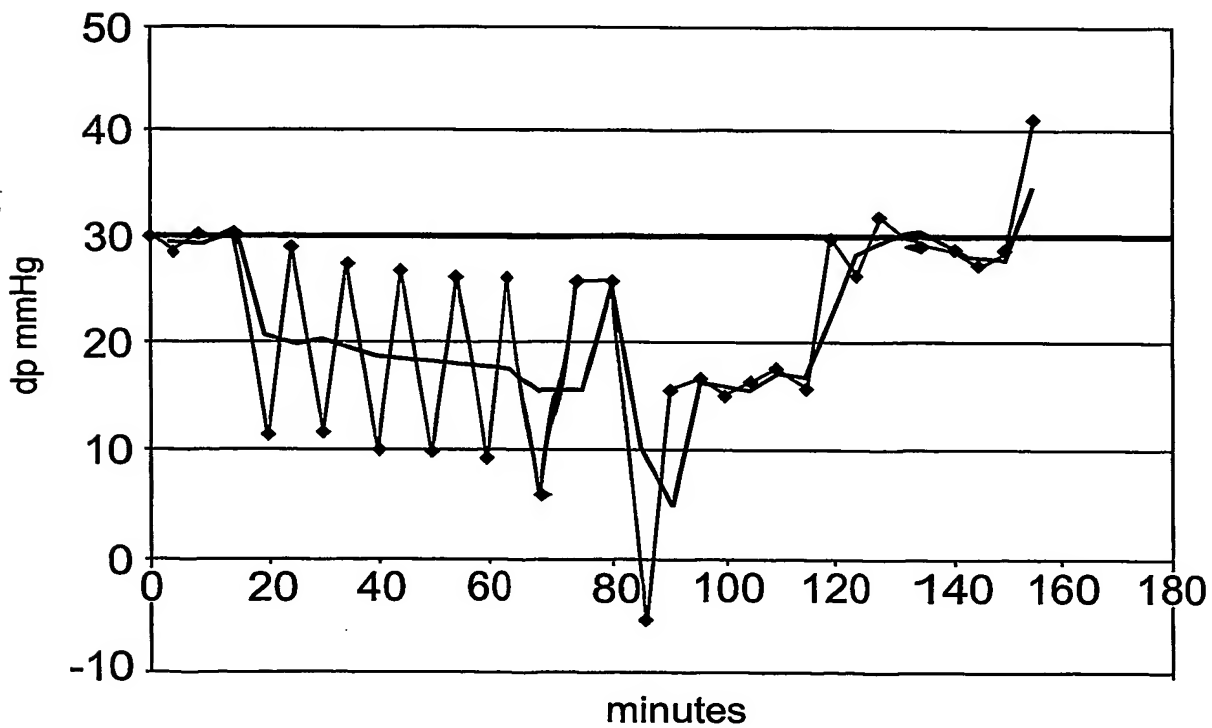
*Fig. 3b**Fig. 4b*

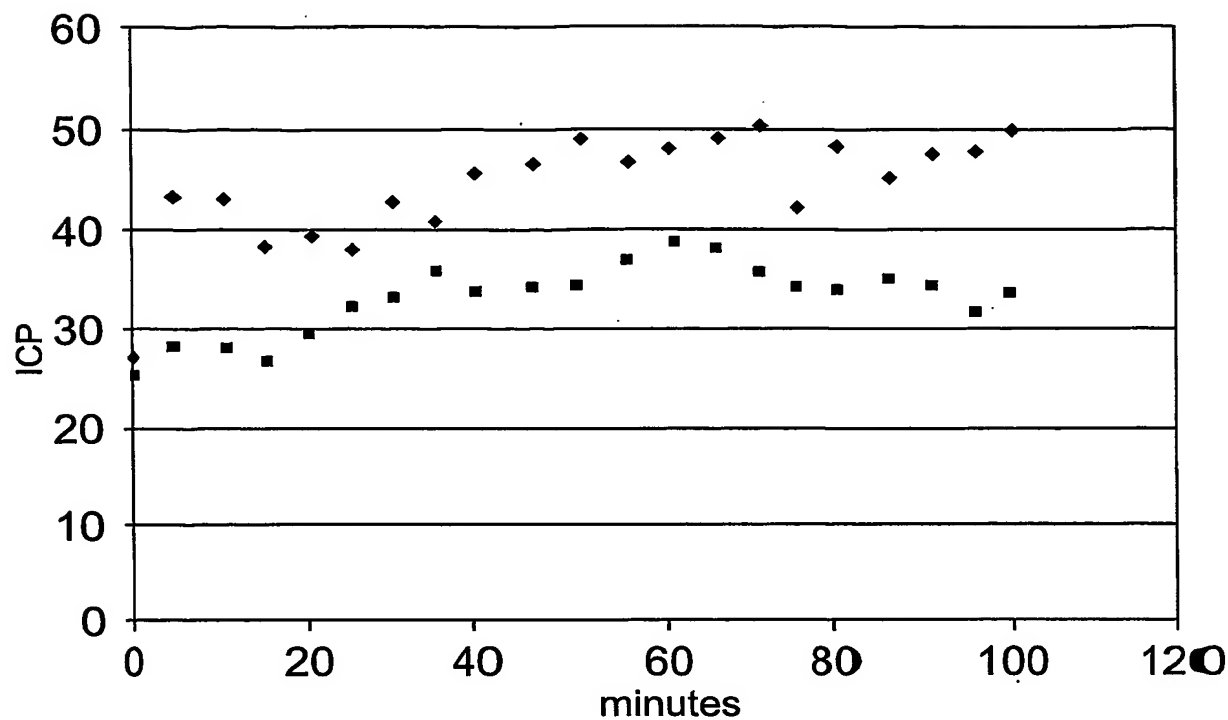
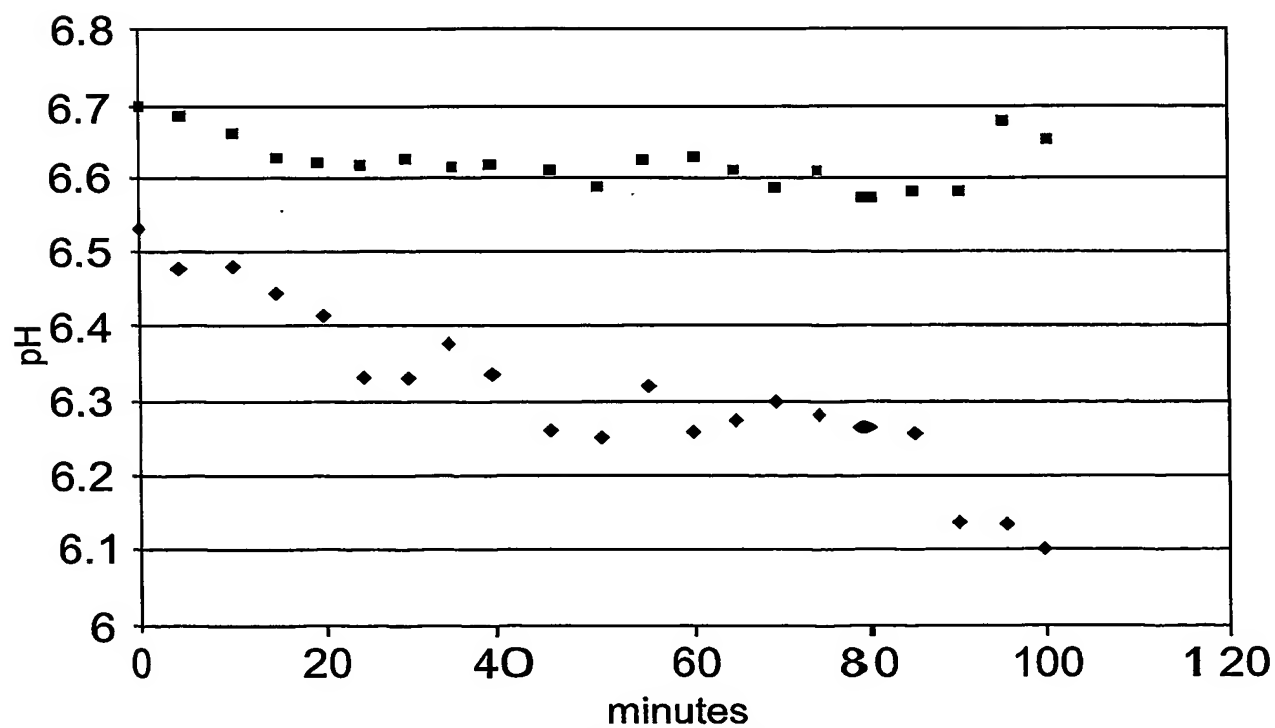
*Fig. 5**Fig. 6*

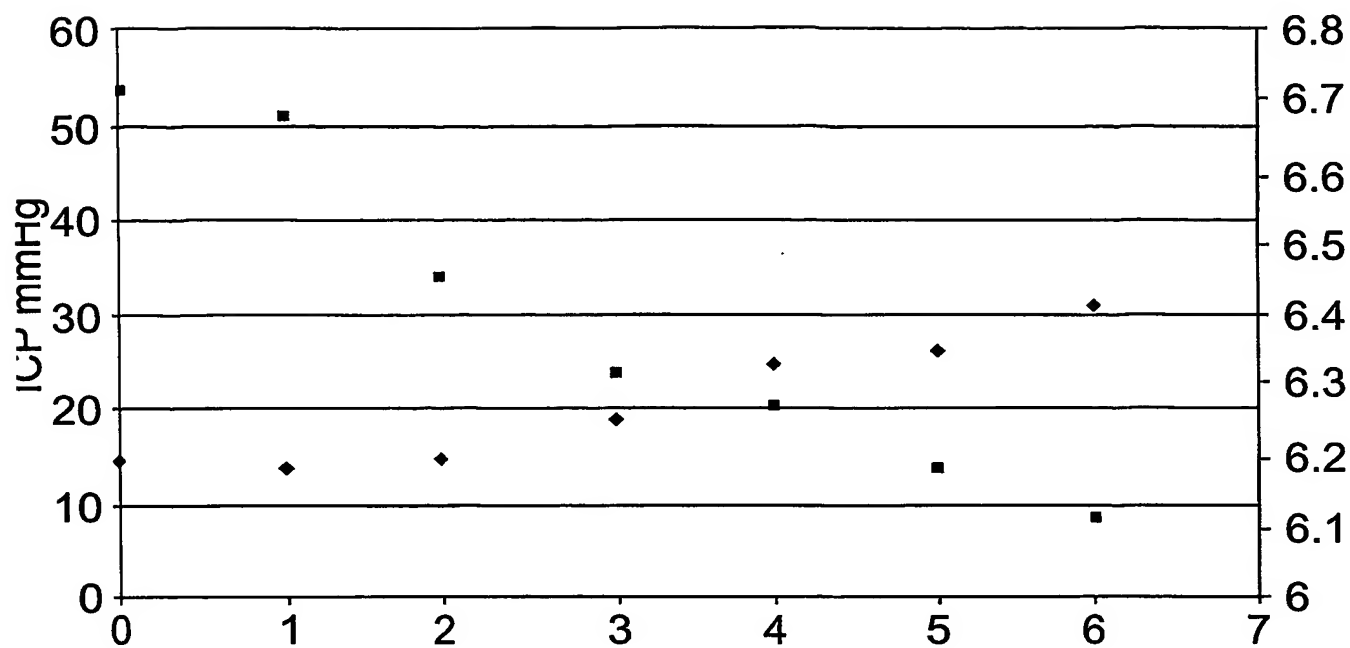
*Fig. 7**Fig. 8*

*Fig. 9**Fig. 10*

*Fig. 11**Fig. 12**Fig. 13*

*Fig. 14**Fig. 15*

*Fig. 16**Fig. 17*

*Fig. 18*

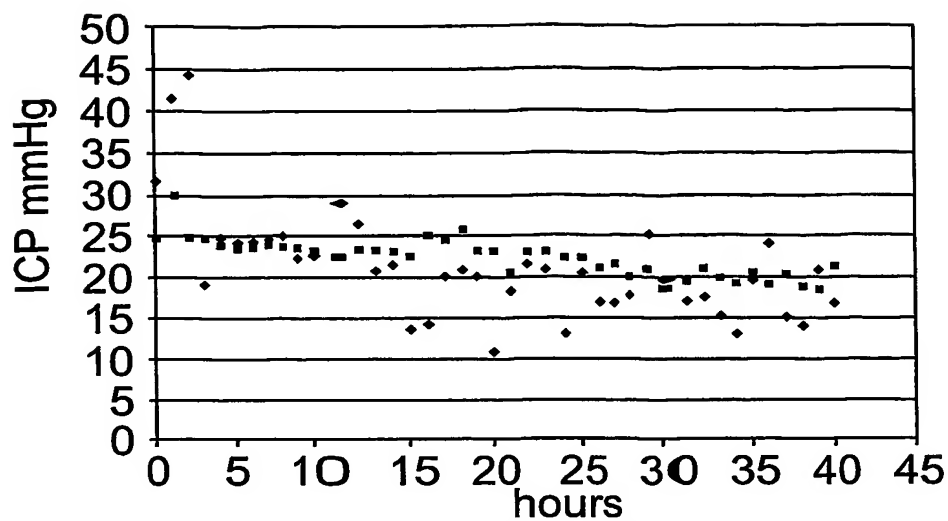
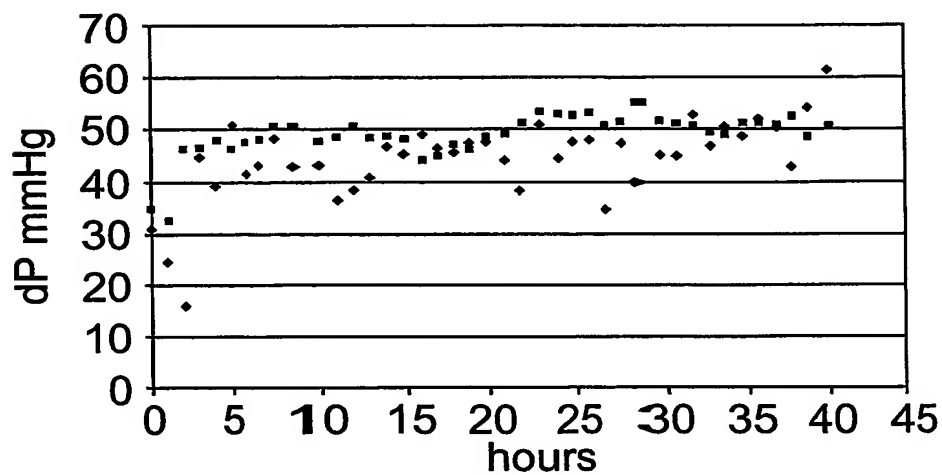
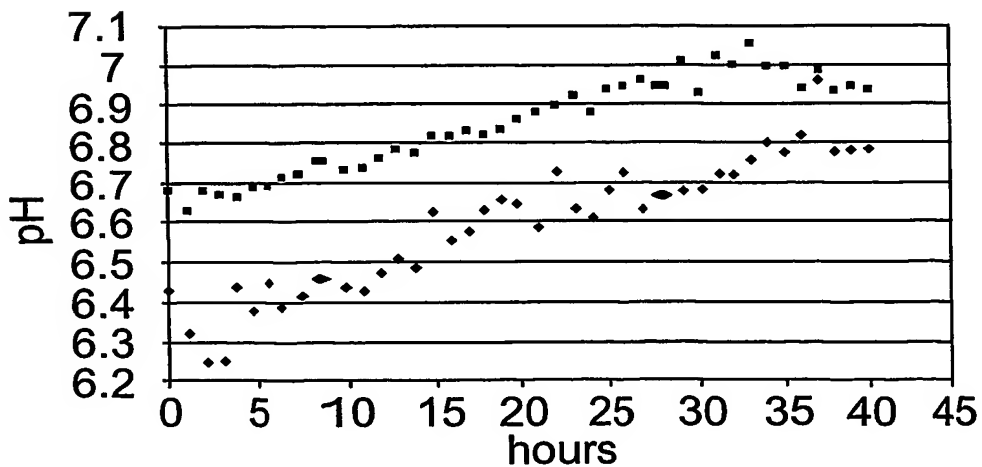
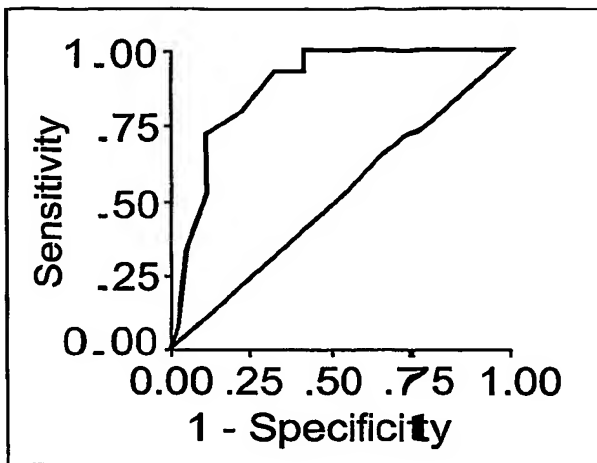
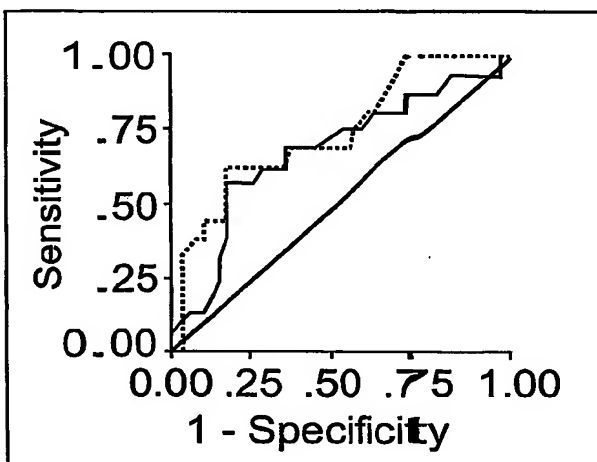
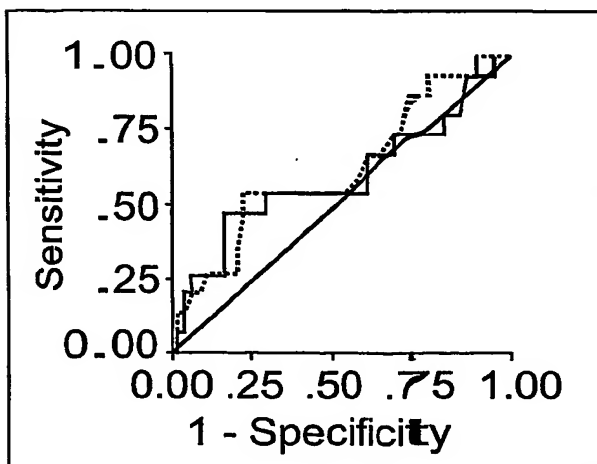
*Fig. 19**Fig. 20**Fig. 21*

Fig. 22*Fig. 23*

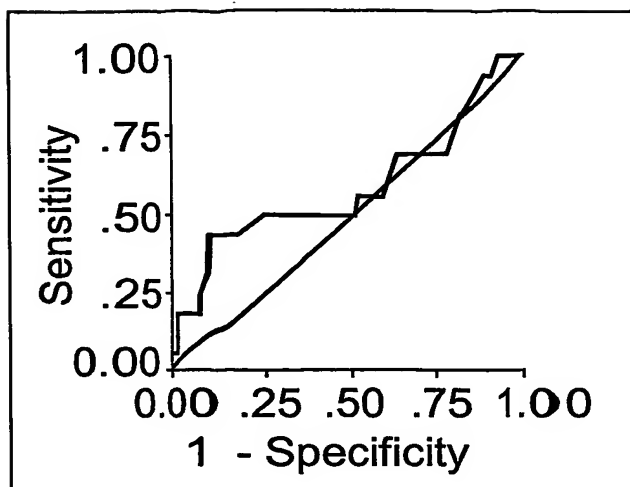
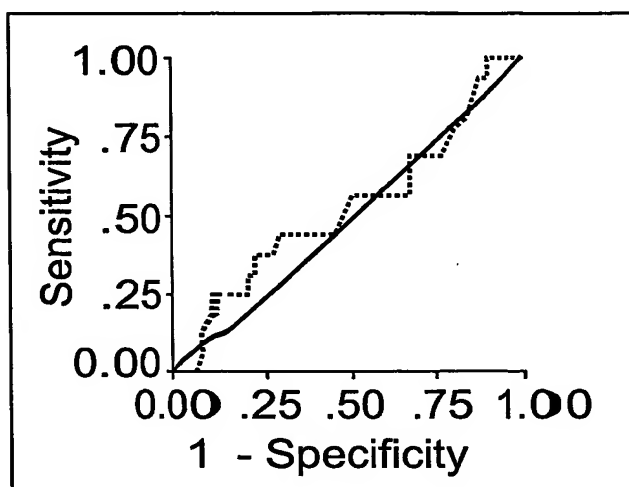
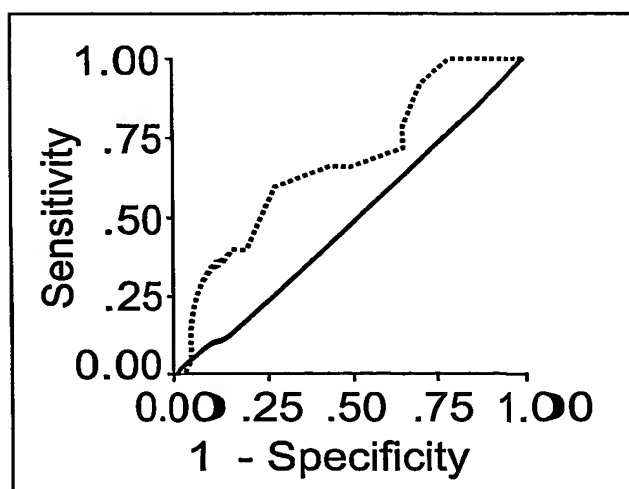
Source of the Curve

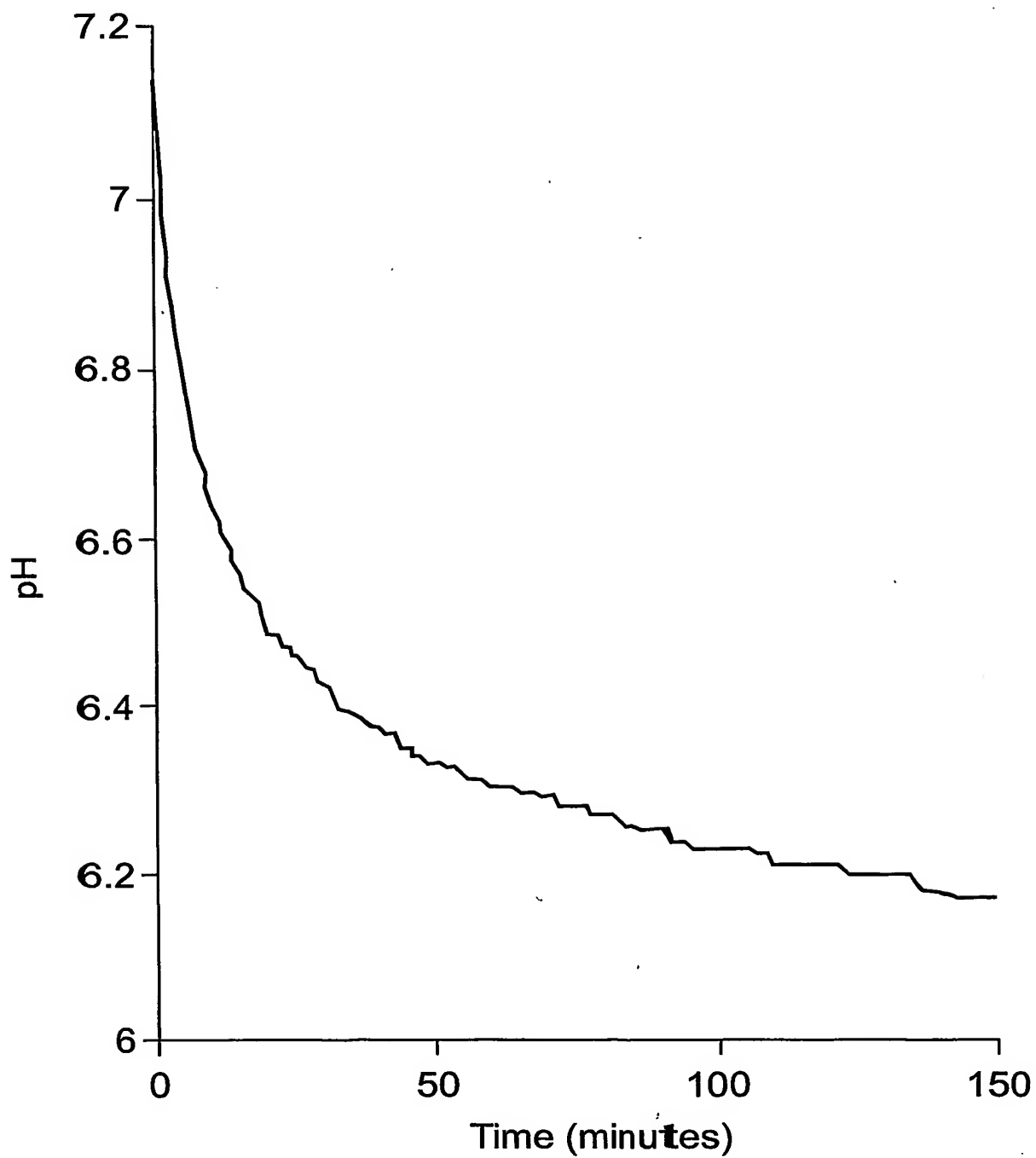
- Reference Line
- - - moving ave. high ICP
- absolute high ICP

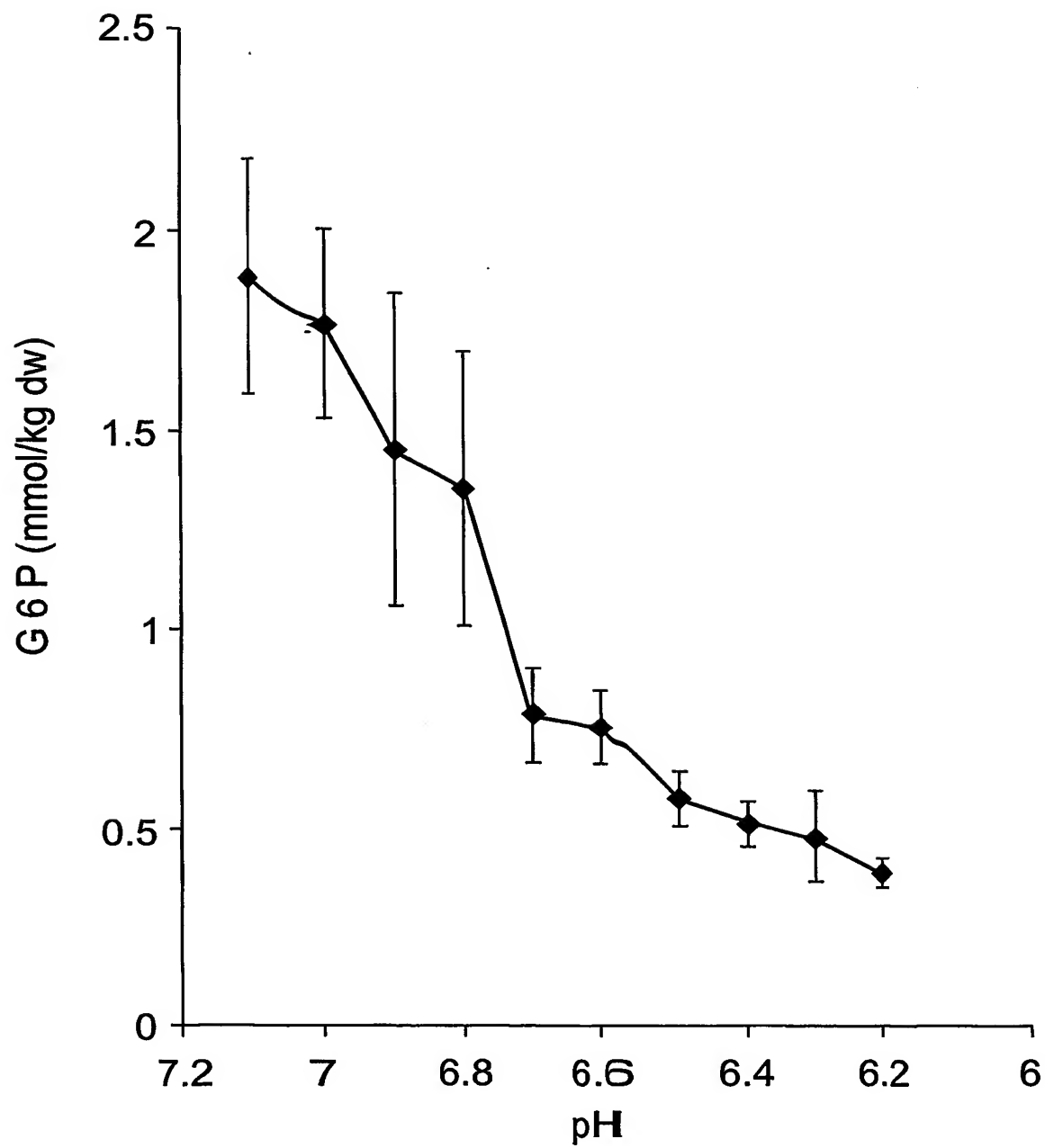
Fig. 24

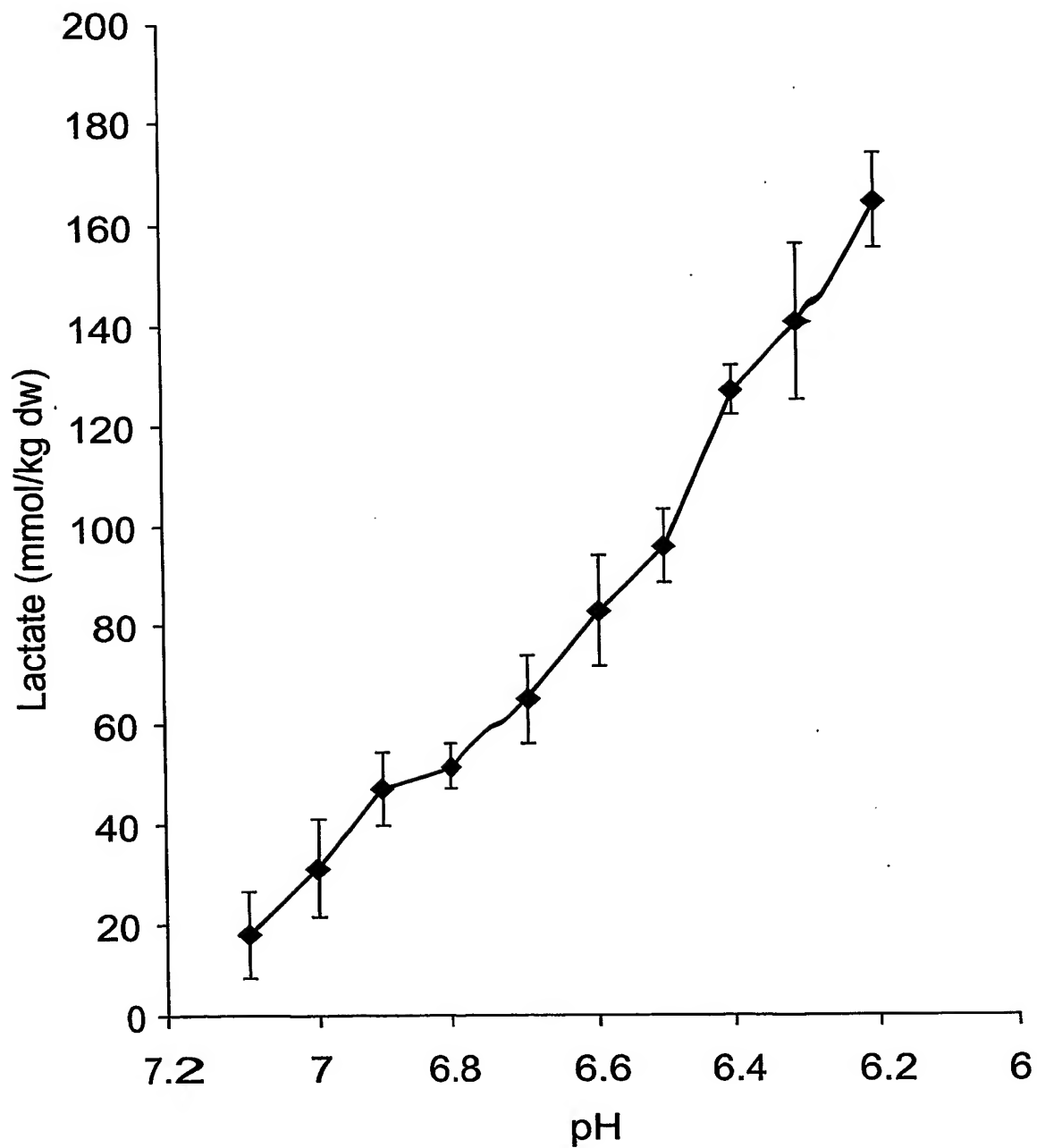
Source of the Curve

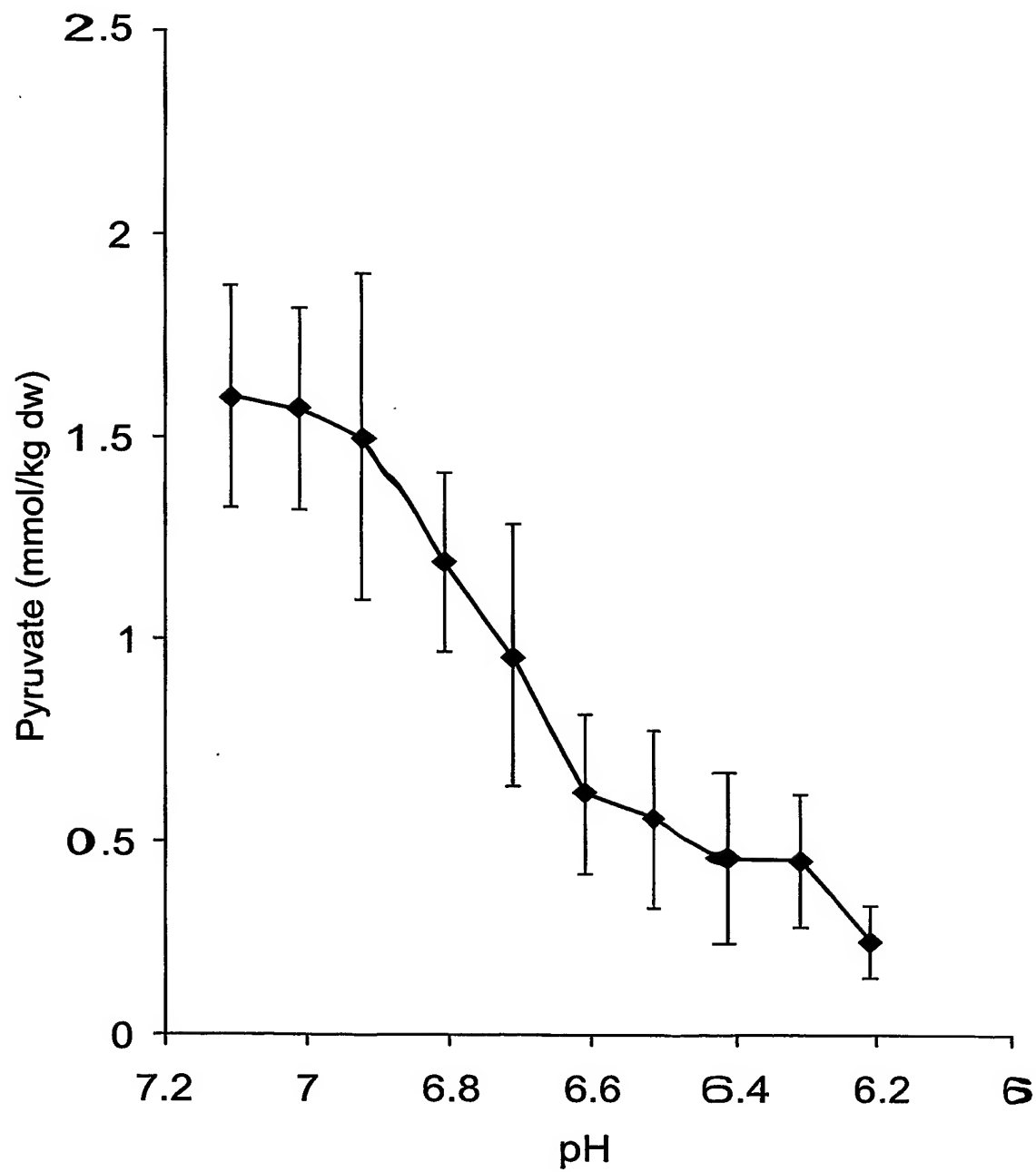
- Reference Line
- - - moving average low dP
- absolute low dP

Fig. 25*Fig. 26**Fig. 27*

*Fig. 28*

*Fig. 29*

*Fig. 30*

*Fig. 31*

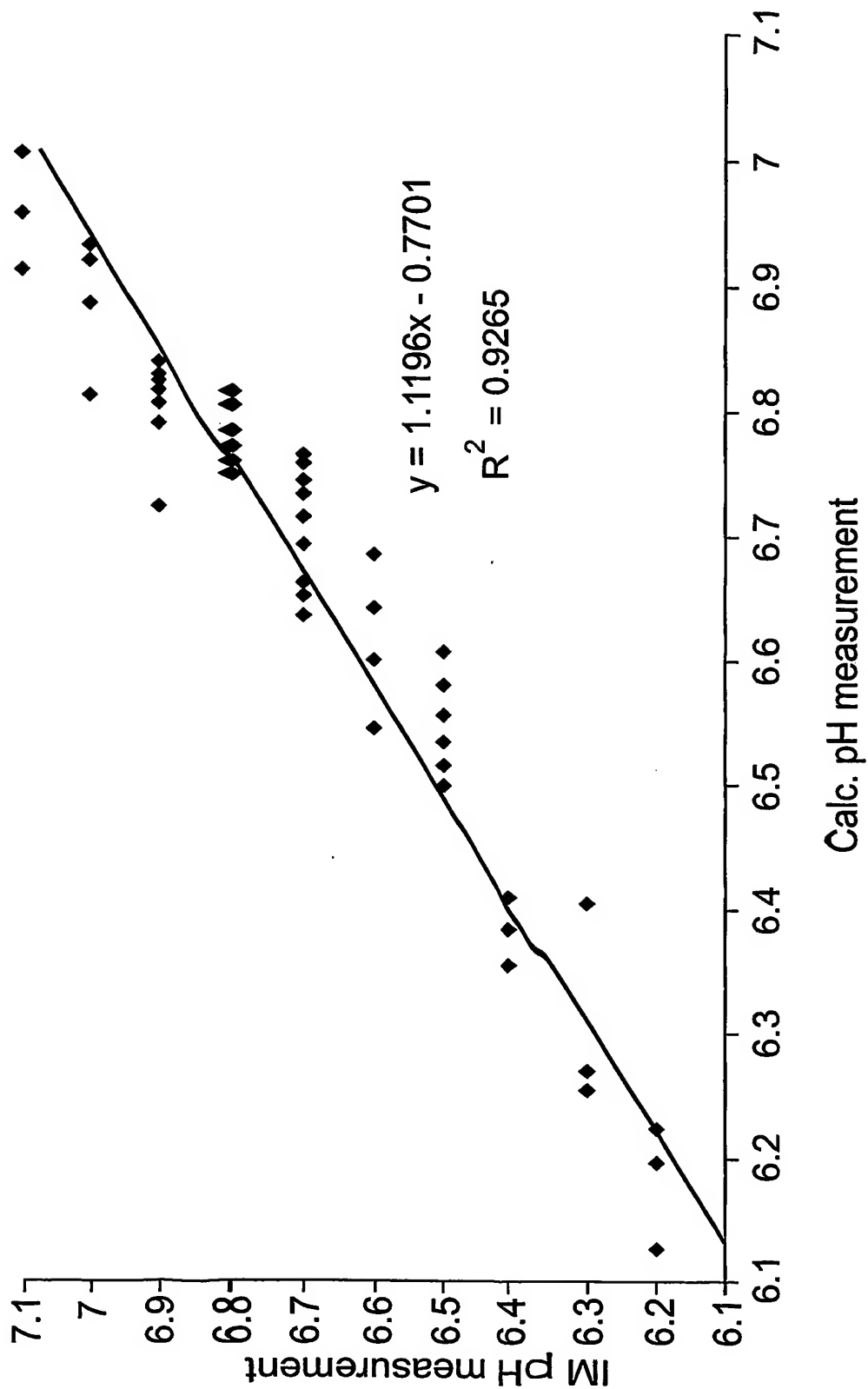


Fig. 32

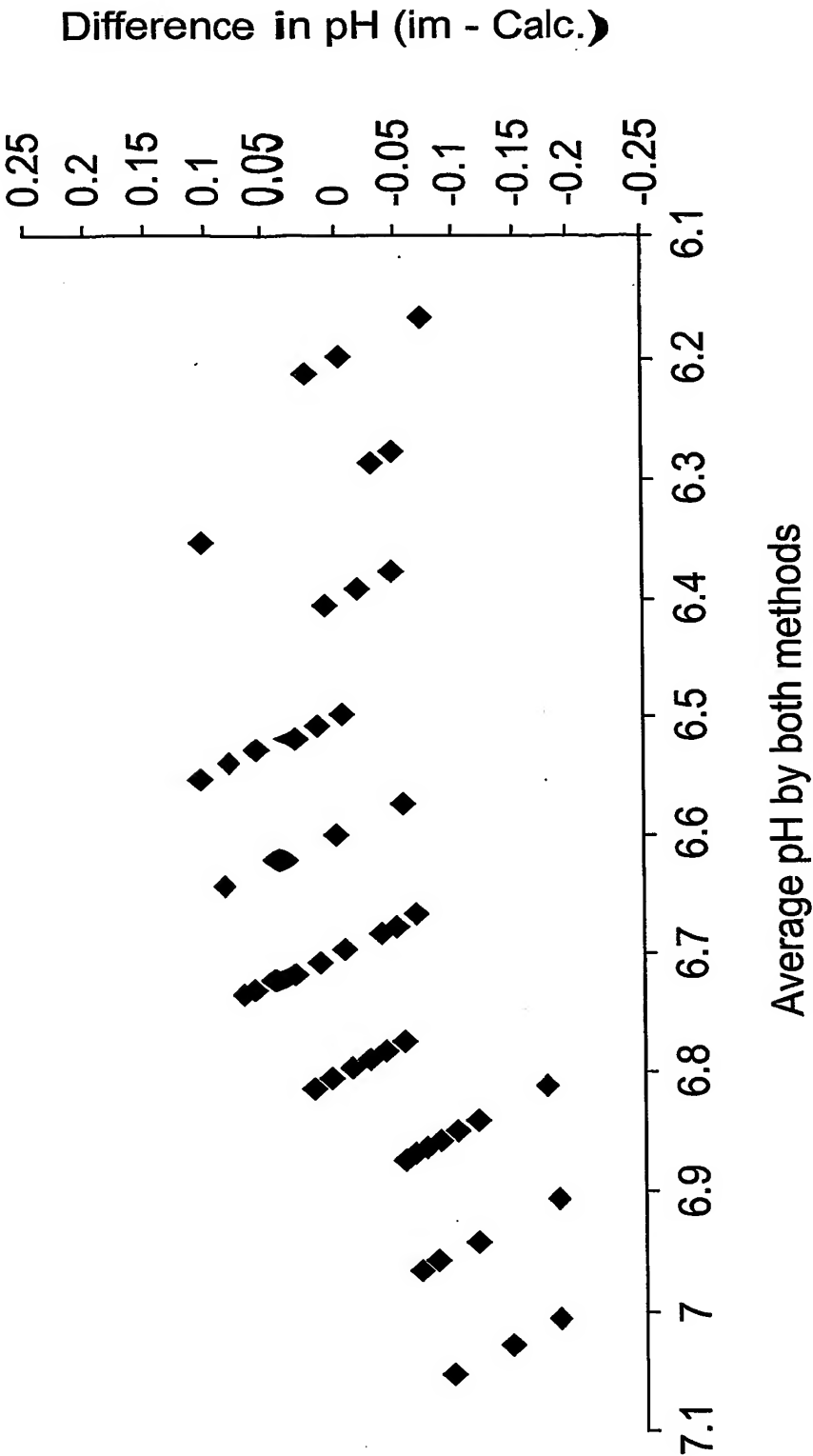
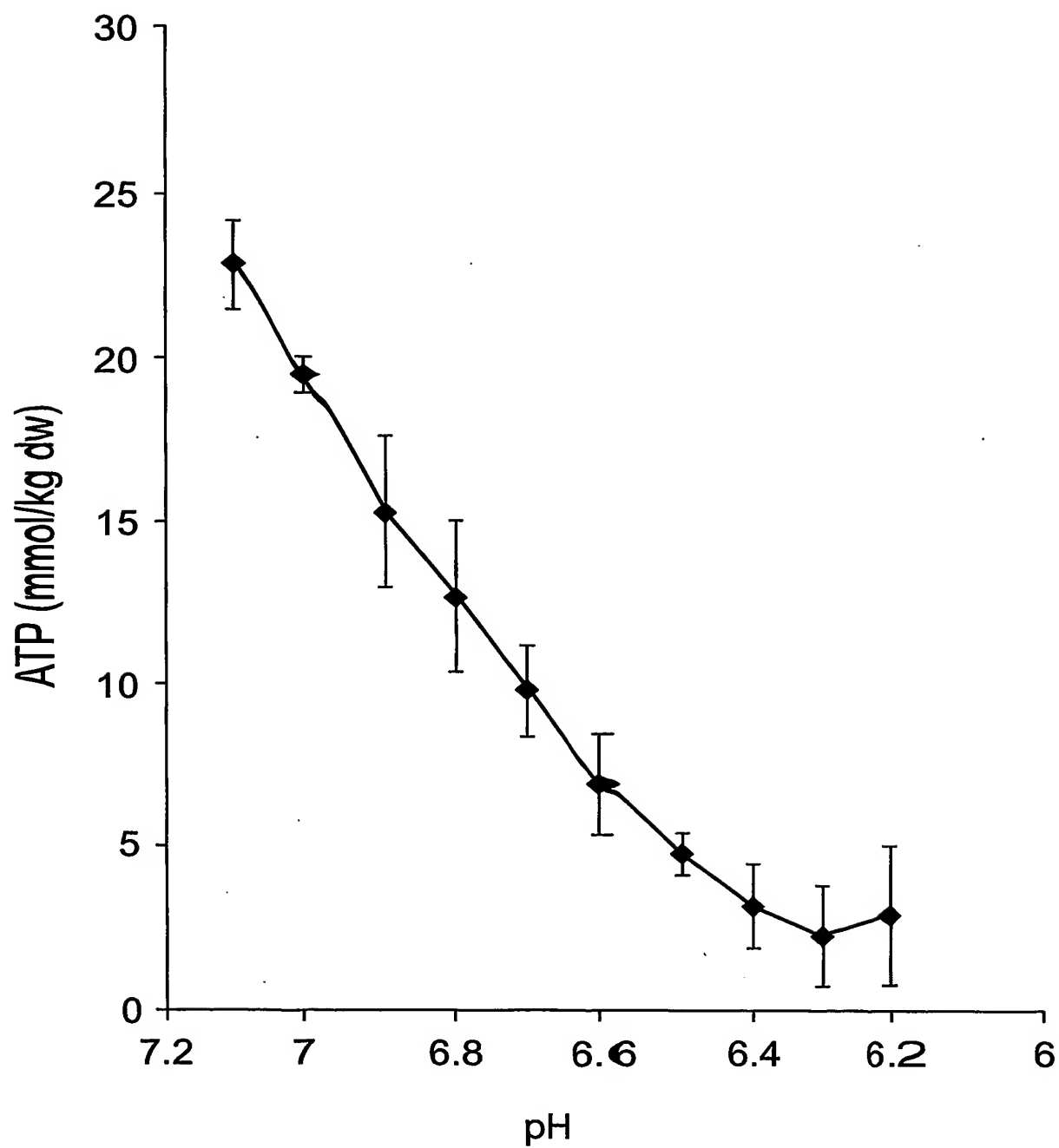
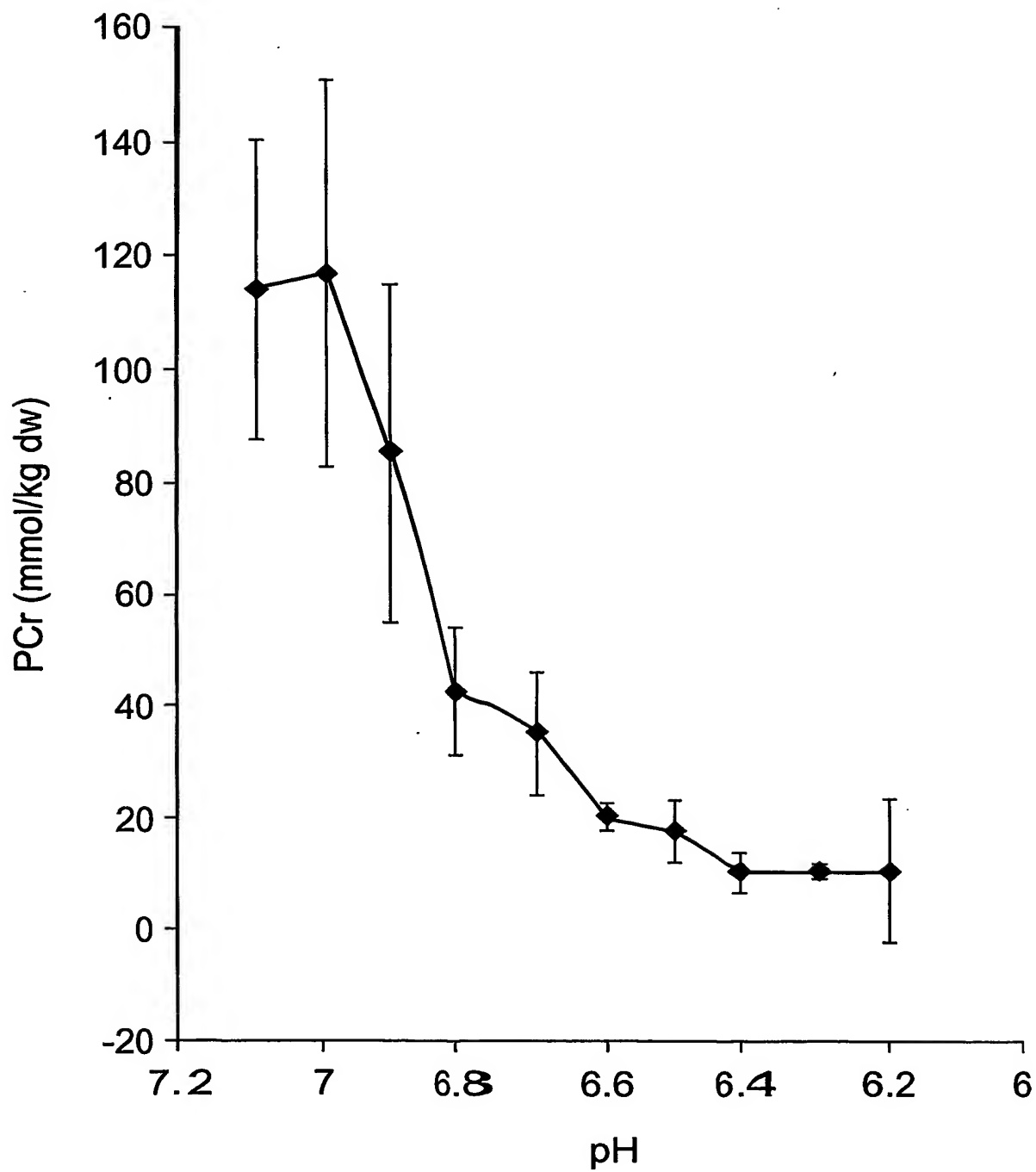


Fig. 33

*Fig. 34*

*Fig. 35*

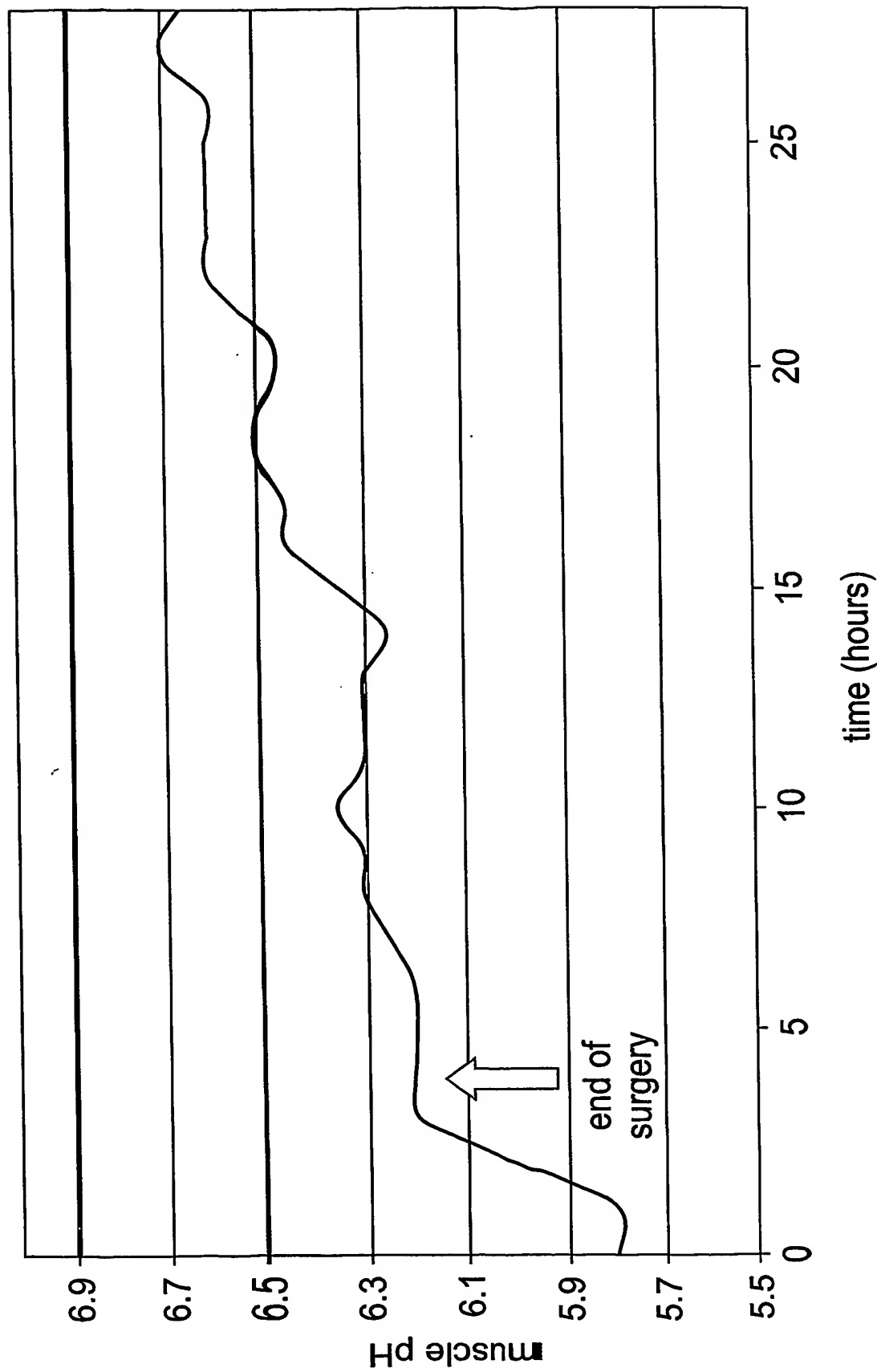


Fig. 36

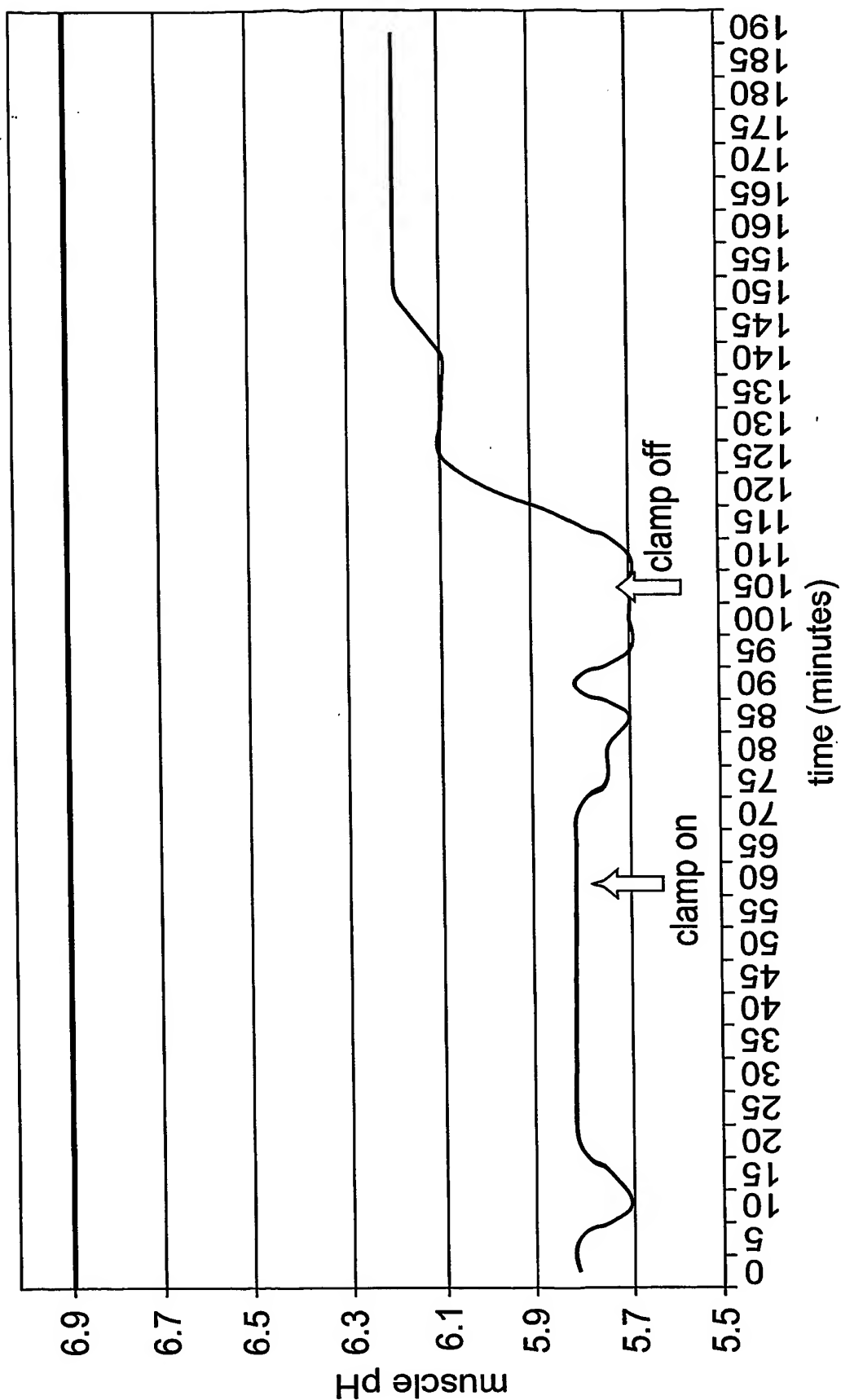


Fig. 37

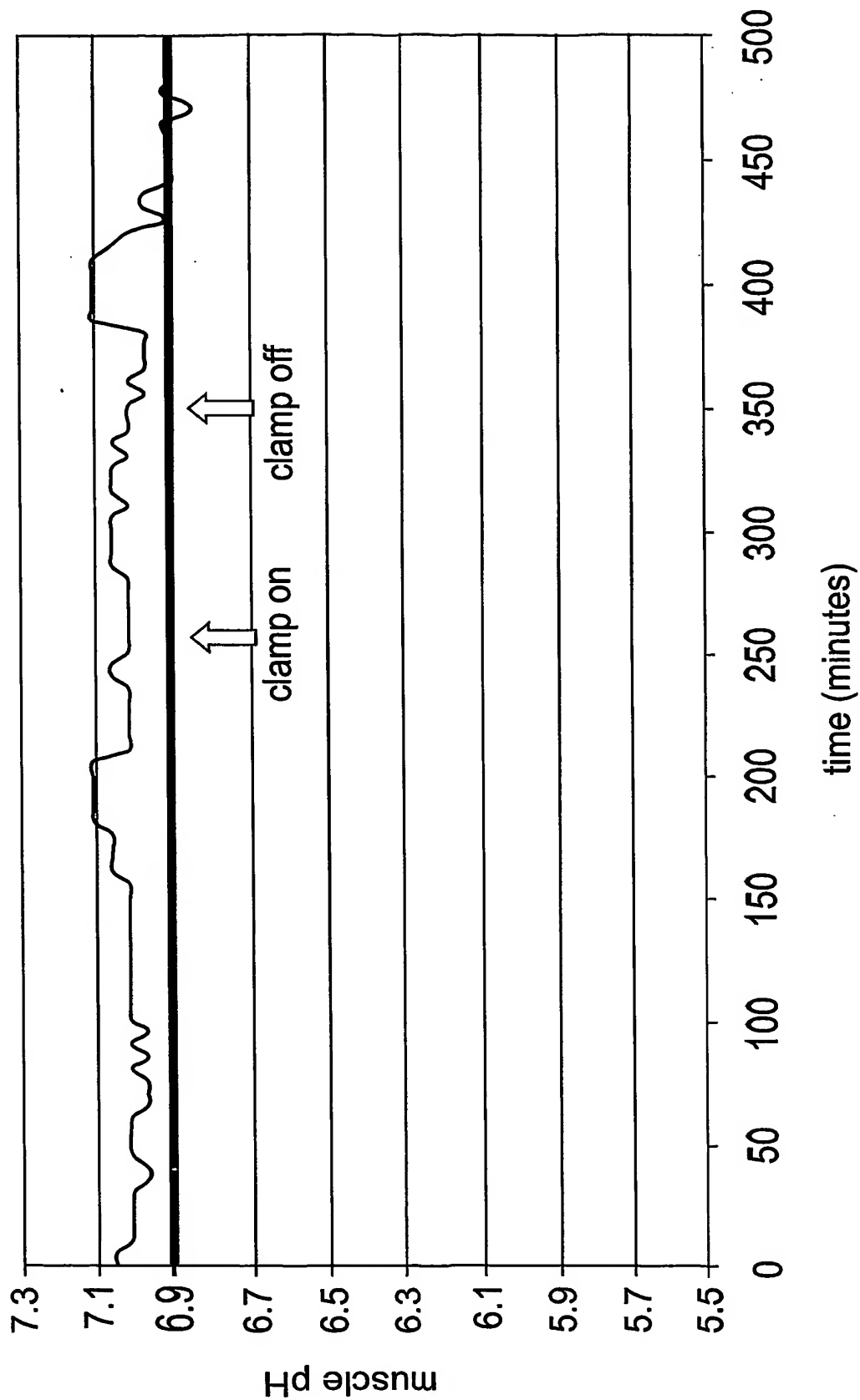


Fig. 38

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 03/03608

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61B5/00 A61B5/03

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, INSPEC, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 92 19150 A (INNERSPACE INC) 12 November 1992 (1992-11-12) page 1, line 9 -page 2, line 4 page 12, line 28 - line 33 page 14, line 4 - line 6 page 15, line 1 - line 2 ---	13,14, 17-19
X	US 3 224 436 A (LE MASSENA ROBERT A) 21 December 1965 (1965-12-21) column 4, line 25 - line 28 column 5, line 36 - line 42; figure 1 ---	13-15,19
A	US 5 158 083 A (SHAHNARIAN ALBERT ET AL) 27 October 1992 (1992-10-27) column 1, line 12 - line 13 column 3, line 35 -column 38 ---	13-15,19
-/-		

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

G document member of the same patent family

Date of the actual completion of the international search

25 November 2003

Date of mailing of the international search report

03/12/2003

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Authorized officer

Knüpling, M

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 03/03608

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>US 5 117 827 A (CLARK CHARLES S ET AL) 2 June 1992 (1992-06-02) column 6, line 24 - line 27 abstract</p> <p style="text-align: center;">-----</p>	<p>13,14, 16-19</p>

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 03/03608

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 1-12, 20-23
because they relate to subject matter not required to be searched by this Authority, namely:
Rule 39.1(iv) PCT - Diagnostic method practised on the human or animal body
surgery
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/GB 03/03608

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9219150	A	12-11-1992	WO 9219150 A1	12-11-1992
US 3224436	A	21-12-1965	DE 1227696 B	27-10-1966
			FR 1323135 A	05-04-1963
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			WO 9105508 A1	02-05-1991
			ZA 9008487 A	28-08-1991
US 5117827	A	02-06-1992	NONE	